Genetic Metabolic Diseases Advisory Committee (GeMDAC)
FDA Opening Remarks

NDA 214927 Arimoclomol for the Treatment of Adults and Pediatric Patients 2 Years of Age and Older With Niemann-Pick Disease, Type C

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US Food and Drug Administration
August 2, 2024

Arimoclomol

- New molecular entity; orally available small molecule
- Mechanism of action (MOA) has yet to be fully elucidated
  - Applicant proposes that the drug increases the transcription of several genes involved in lysosomal function and facilitates the proper folding and maturation of certain mutant NPC proteins
- Proposed indication
  - Treatment of adults and pediatric patients 2 years of age and older with Niemann-Pick Disease, Type C (NPC)

NPC

- Rare autosomal recessive lysosomal storage disorder
- Bi-allelic mutations in *NPC1* or *NPC2*
- Leads to progressive neurovisceral symptoms
- Median age of death: 13 years
- **Significant unmet need**
  - Current standard of care is primarily supportive
  - Miglustat used off-label in U.S.

Regulatory Framework

- Substantial Evidence of Effectiveness
  - Generally interpreted as a requirement for two adequate and well-controlled clinical investigations
  - FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA has determined that such data are sufficient
    - Approach often used when it is not feasible or practicable to conduct more than a single adequate and well-controlled trial
  - Confirmatory evidence substantiates the trial results
    - Quantity and sources of evidence may vary
  - FDA exercises flexibility within this regulatory framework

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Draft Guidance for Industry December 2019 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry September 2023 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical

NDA 214927 Original Submission

- Single adequate and well-controlled clinical trial Study CT-ORZY-NPC-002 (NPC-002) and proposed confirmatory evidence from in vitro, animal, and clinical pharmacology data
- The primary analysis compared arimoclomol to placebo on the mean change in baseline to month 12 on the 5-domain NPC Clinical Severity Scale (5DNPCCSS)—swallowing, speech, fine motor, ambulatory, and cognitive functioning
- Complete Response June 2021:
  - Concerns with the 5DNPCCSS, particularly swallow and cognition domains
  - Concerns with the prespecified primary analysis for the 5DNPCCSS endpoint and uncertainty regarding the estimated treatment effect
  - Weak and contradictory confirmatory evidence of effectiveness

NDA 214927 Resubmission

- Resubmission December 2023
  - Modified analysis of the primary endpoint (post hoc)
    - Removed cognition domain, rescored swallow domain
    - Rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCCSS)
  - Additional confirmatory evidence
    - Clinical data
    - Non-clinical studies

Data for Evaluation

- Post hoc R4DNPCCSS Endpoint: point estimate of treatment difference ranges from -1.5 to -1.2, depending on the analysis methods used; results favor the arimoclomol arm
  - Concerns regarding the validity of the endpoints
- Additional nonclinical and clinical data
  - Nonclinical:
    - Proposed MOA
    - In vitro data with arimoclomol with or without miglustat
    - Data from NPC1$^{-/-}$ and NPC1$^{nmf/nmf}$ mice treated with arimoclomol and/or miglustat
  - Clinical:
    - Open-label extension of study NPC-002 (NPC-002 OLE)
    - Comparison of NPC-002 OLE to natural history data from the National Institutes of Health (NIH NHS)
    - Observational study NPC-001
    - Data from patients treated with arimoclomol under expanded access protocols
    - Clinical pharmacology data

Key Efficacy Issues for Discussion

- Uncertainty regarding the estimated treatment effect on the mean change from baseline in the 5DNPCCSS and the R4DNPCCSS
- Validity of the 5DNPCCSS and the R4DNPCCSS
- Adequacy of the additional clinical and nonclinical data to support the effectiveness of arimoclomol
- The strength of the overall evidence to support the efficacy of arimoclomol in NPC

Discussion and Voting Questions

- DISCUSSION: Discuss your assessment of the efficacy results of trial NPC-002. In your discussion, please comment on:
  - The 5-domain Niemann-Pick disease type C Clinical Severity Scale (5DNPCCSS) and the rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCCSS).
  - Your assessment of whether the trial results demonstrate a treatment effect of arimoclomol on the treatment of Niemann-Pick disease type C (NPC).
- DISCUSSION: Discuss your assessment of other data (specifically the additional clinical and nonclinical data) with respect to support for the effectiveness of arimoclomol.
- VOTE: Do the results of trial NPC-002 in concert with the other data (clinical and nonclinical in particular) support a conclusion that arimoclomol is effective in the treatment of patients with NPC? Provide a rationale for your vote.
  - If you voted no, provide recommendations for additional data that may support a conclusion that arimoclomol is effective.

Overview of the Clinical Program

Arimoclomol for the Treatment of Niemann Pick disease, Type C (NPC)

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Clinical Reviewer
Division of Rare Diseases and Medical Genetics

Niemann Pick Disease, Type C (NPC)

- Rare autosomal recessive lysosomal storage disorder
- Bi-allelic mutations in *NPC1* or *NPC2*
- Dysfunctional NPC1 or NPC2 leads to impaired intracellular metabolism of cholesterol, sphingolipids and glycosphingolipids
  → Storage of these lipids in affected cells; primarily brain, liver, spleen and lungs

Applicant Proposed Mechanism of Action of Arimoclomol

Increases the transcription of several genes involved in lysosomal function and facilitates the proper folding and maturation of certain mutant NPC proteins.

Clinical Manifestations

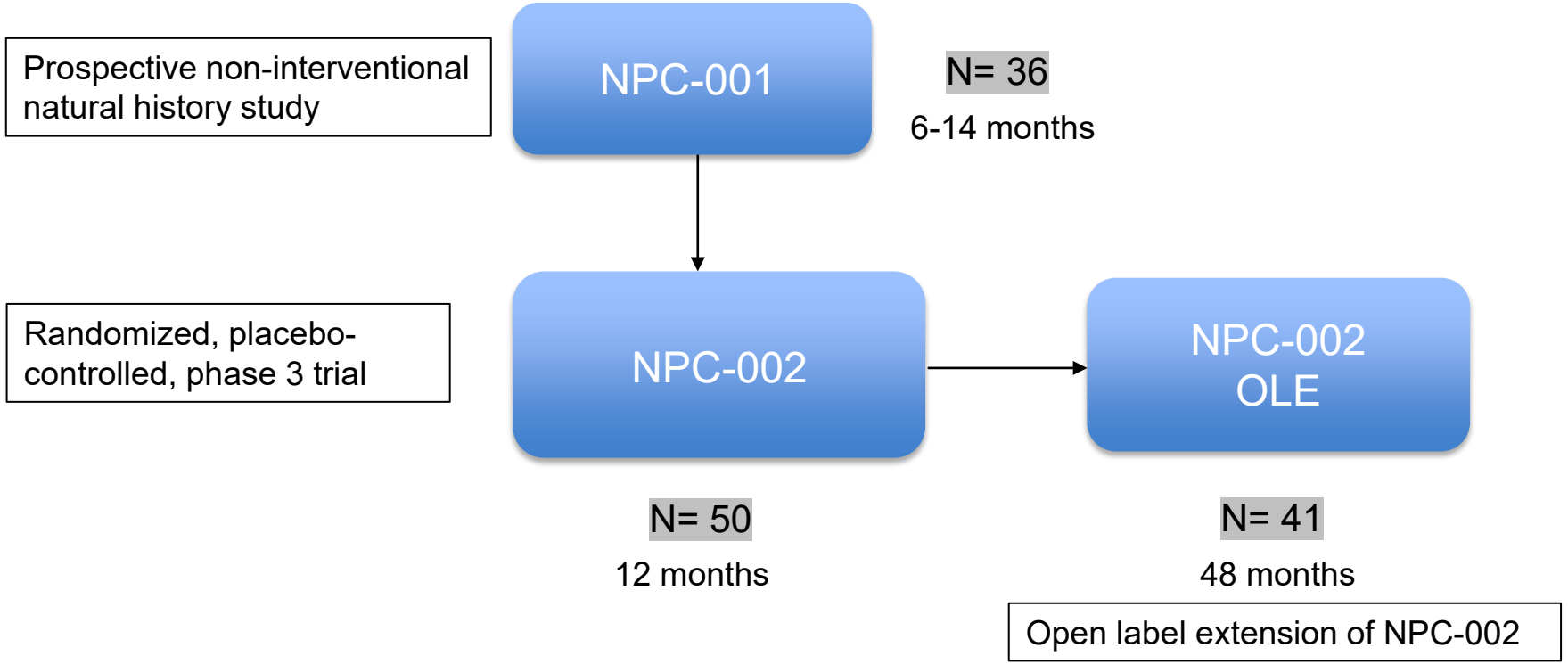
- Primary manifestations, severity, and rate of progression are highly variable
  - From severe systemic disease with death in neonatal period to adult onset with chronic progressive symptoms
- With disease onset < 2 years of age (early infantile) predominant visceral symptoms
- With onset > 2 years of age, symptoms are primarily neurodegenerative and include the following:
  - Hypotonia
  - Developmental delays
  - Loss of gross and fine motor skills
  - Dysphagia
  - Dysarthria
  - Ataxia
  - Epilepsy
  - Cataplexy
  - Vertical supranuclear gaze palsy
  - Psychiatric symptoms/cognitive impairment

Unmet Need

- Current standard of care is primarily supportive
- Miglustat used off-label in U.S.
- Unmet need for treatment options for this devastating disorder
  - Median age of death: 13 years, typically due to respiratory failure (infection and/or aspiration)
  - No significant change in survival over last 20 years[1]
  - Patients and caregivers eager for treatments that will improve the symptoms or slow the progression of NPC[2]

[1] Bianconi, SE, DI Hammond, NY Farhat, A Dang Do, K Jenkins, A Cougnoux, K Martin, and FD Porter, 2019, Evaluation of age of death in Niemann-Pick disease, type C: Utility of disease support group websites to understand natural history, Mol Genet Metab, 126(4):466-469.
[2] EL-PFDD VoP, 2019, Voice of the Patient Report: Condition-Specific Meeting Reports and Other Information Related to Patients' Experience https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience.

Clinical Studies Relevant to the Evaluation of Efficacy



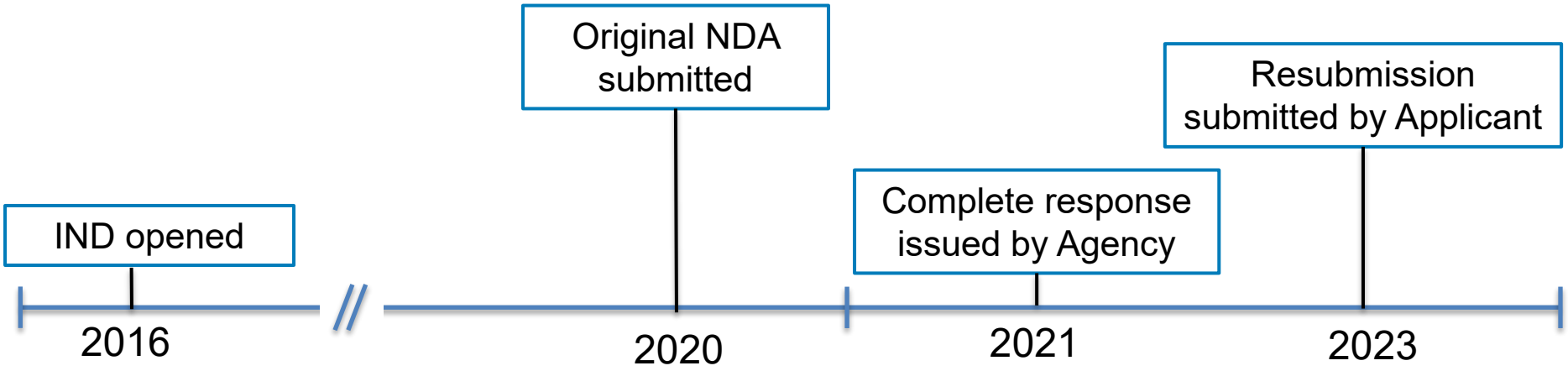
Primary Endpoint for NPC-002

Change in 5DNPCCSS scores from baseline to end of double-blind period

- Niemann Pick disease, Type C Clinical Severity Scale (NPCCSS)
  - Used broadly in clinical care to characterize signs and symptoms of NPC over time
  - Original version has 17 domains encompassing broad range of neurovisceral symptoms of NPC years[1]
- 5-domain NPCCSS **(5DNPCCSS)**
  - 5 domains of NPCCSS considered meaningful to patients, caregivers and clinical experts: cognition, ambulation, fine motor, speech, swallow[2]

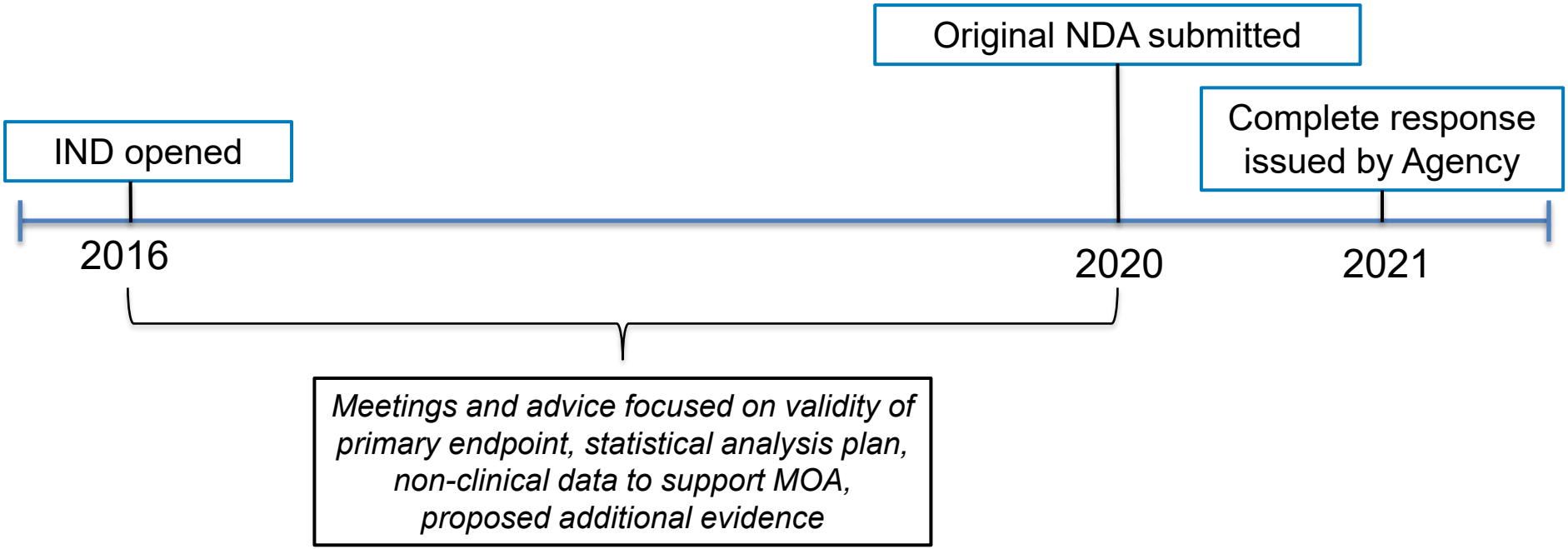
[1] Yanjanin, NM, JI Velez, A Gropman, K King, SE Bianconi, SK Conley, CC Brewer, B Solomon, WJ Pavan, M Arcos-Burgos, MC Patterson, and FD Porter, 2010, Linear clinical progression, independent of age of onset, in Niemann-Pick disease, type C, Am J Med Genet B Neuropsychiatr Genet, 153B(1):132-140.
[2]Patterson MC, Lloyd-Price L, Guldberg C, Doll H, Burbridge C, Chladek M, íDali C, Mengel E, Symonds T. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis. 2021 Feb 12;16(1):79. doi: 10.1186/s13023-021-01719-2. PMID: 33579322; PMCID: PMC7881637.

Regulatory History



IND Investigational New Drug Application
NDA New Drug Application
MOA Mechanism of action

Regulatory History- Original Submission

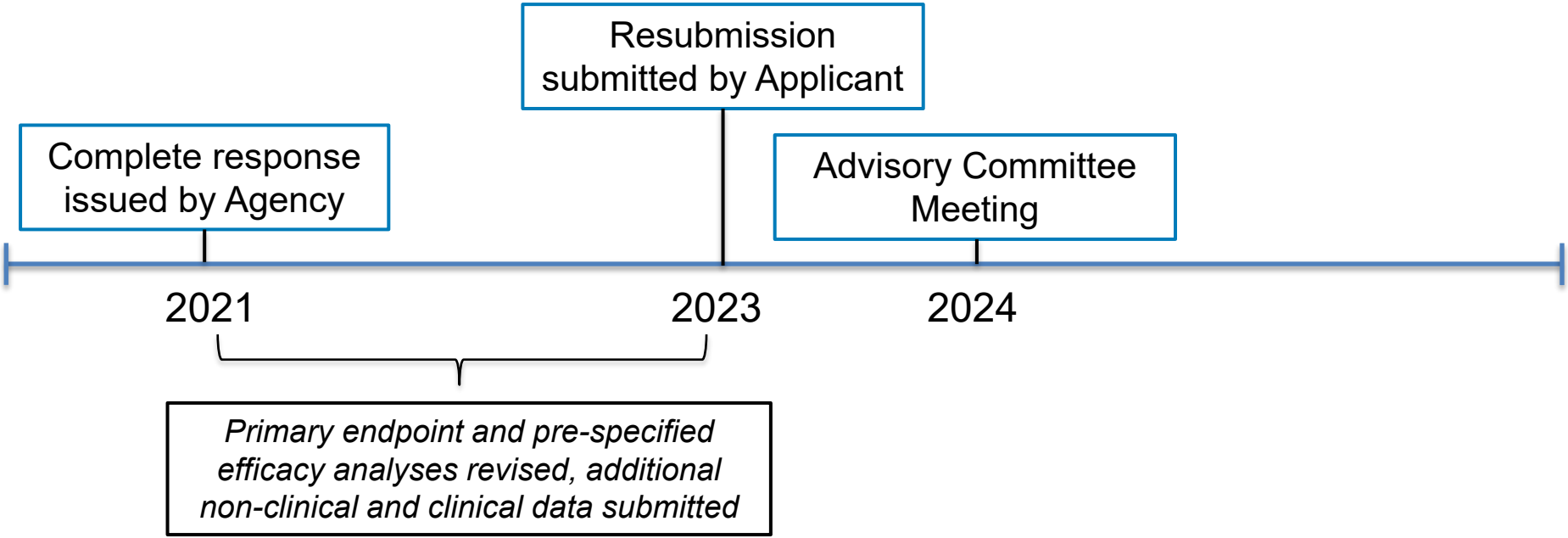


IND Investigational New Drug Application
NDA New Drug Application
MOA Mechanism of action

Main Deficiencies in Complete Response Letter

1. Validity of the 5DNPCCSS, specifically the cognition and swallowing domains
2. Concerns with the Applicant's prespecified efficacy analysis and uncertainty regarding the estimated treatment effect
3. Adequacy of the confirmatory evidence to support a true drug effect

Regulatory History- Resubmission



Applicant NDA Resubmission

- Modified primary endpoint

Change in R4DNPCCSS scores from baseline to end of the double-blind period

  - Removed cognition domain, rescored swallow domain
- Post hoc efficacy analyses
- Additional clinical and clinical pharmacology data
- Non-clinical studies

Primary Efficacy Results in Pivotal Trial

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Study CT-ORZY-NPC-002 (Study NPC-002)

- Randomized (2:1), 12-month double-blind (DB), placebo-controlled, superiority study in subjects with NPC
  - Arimoclomol (N=34), placebo (N=16)
  - Randomization was stratified by miglustat use at baseline (yes/no)
  - Most subjects (39/50, 78%) received off-label miglustat as part of clinical care
- **The prespecified primary efficacy endpoint is change from baseline to month 12 in the 5DNPCCSS score**
  - 5DNPCCSS score is the sum of scores from five domains (speech, swallow, ambulation, cognition, fine motor skills) in NPC Clinical Severity Scale (NPCCSS)
  - 0 to 25 scale (higher score indicating worse outcome)

“Early Escape” and Subject Disposition

- Subjects on either arm meeting “early escape” criteria due to fast disease progression were allowed to take an escape route where they were treated with open-label arimoclomol for the remaining part of the 12-month DB phase
- Two subjects in the arimoclomol arm took an “early escape” route
- 17.6% of the subjects in the arimoclomol arm and 6.2% in the placebo arm discontinued the study
  - In the arimoclomol arm, one subject died, three subjects discontinued the study due to adverse events, and one early escaped subject discontinued after reaching the worst score

Subject Disposition in 12-Month DB Phase

Description	Arimoclomol N (%)	Placebo N (%)
Subjects randomized	34 (100)	16 (100)
Completed blinded phase		
Yes	27 (79.4)	15 (93.8)
No	7 (20.6)	1 (6.2)
Early escape [1]	2 (5.9)	0 (0.0)
Reason for study discontinuation		
Withdrawal by parent/guardian	1 (2.9)	0 (0.0)
Death	1 (2.9)	0 (0.0)
Safety reasons	3 (8.8)	0 (0.0)
IMP stop criteria met [2]	0 (0.0)	1 (6.2)

Source: Summary of Clinical Efficacy in original submission (Table 2-8).
[1] After taking early escape route, one subject discontinued the study prior to 12 months.
[2] Due to worsening of epilepsy, IMP administration was not possible.
Abbreviations: IMP, investigational medicinal product; DB, double-blind.

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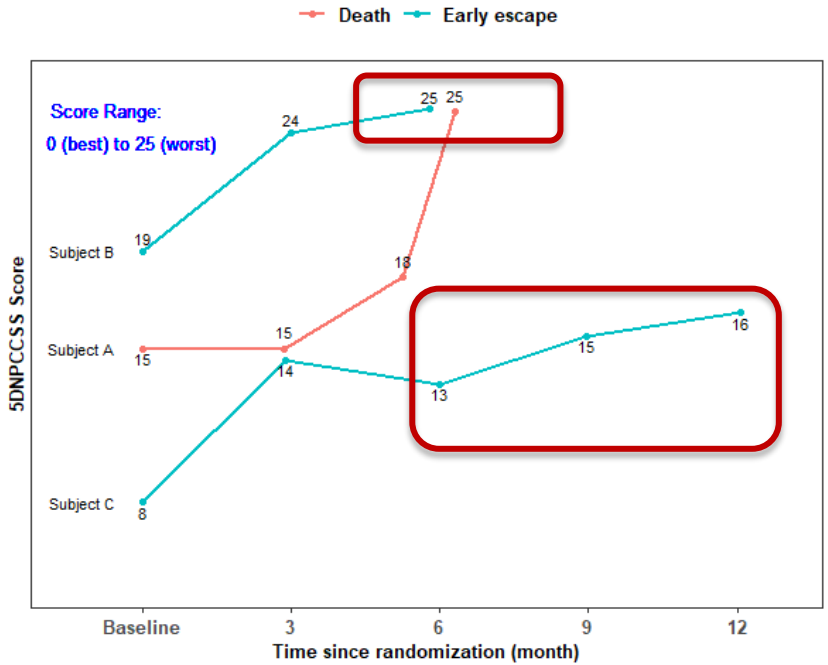
Efficacy Results in Original Submission

Prespecified Primary Analysis in Original Submission

- Mixed model for repeated measures (MMRM)
  - Includes treatment, visit (months 3, 6, 9, and 12), treatment-by-visit interaction, baseline miglustat use (yes/no), and baseline 5DNPCCSS score
  - Unstructured variance-covariance matrix for repeated measures within a subject
- Estimated treatment difference of -1.4 (95% CI: -2.76, -0.03; p-value=0.0456) meets the statistical significance level (two-sided p-value < 0.05)
- However, the primary analysis has limitations:
  - Did not use the data after "early escape"
  - Did not use the last measurement for the subject who died

Limitations of Prespecified Primary MMRM Analysis



Source: FDA's figure

- **Excludes data in the red boxes**
  - Subject A: death after Month 6
  - Subjects B and C: early escape after Month 3
- Treats 5DNPCCSS scores at the visits after early escape or death as missing, and assumes these subjects have similar scores as others at these visits.

FDA's Post Hoc Analyses

- FDA conducted post hoc analyses including the data in the red boxes in the previous slide. The estimated treatment differences are:
  - FDA's MMRM: -0.97 (95% CI: -2.55, 0.62)
  - FDA's ANCOVA: -1.17 (95% CI: -2.65, 0.31)
- These analyses provide smaller treatment difference estimates and wider confidence intervals compared to those from the prespecified analysis.

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Efficacy Results in Resubmission

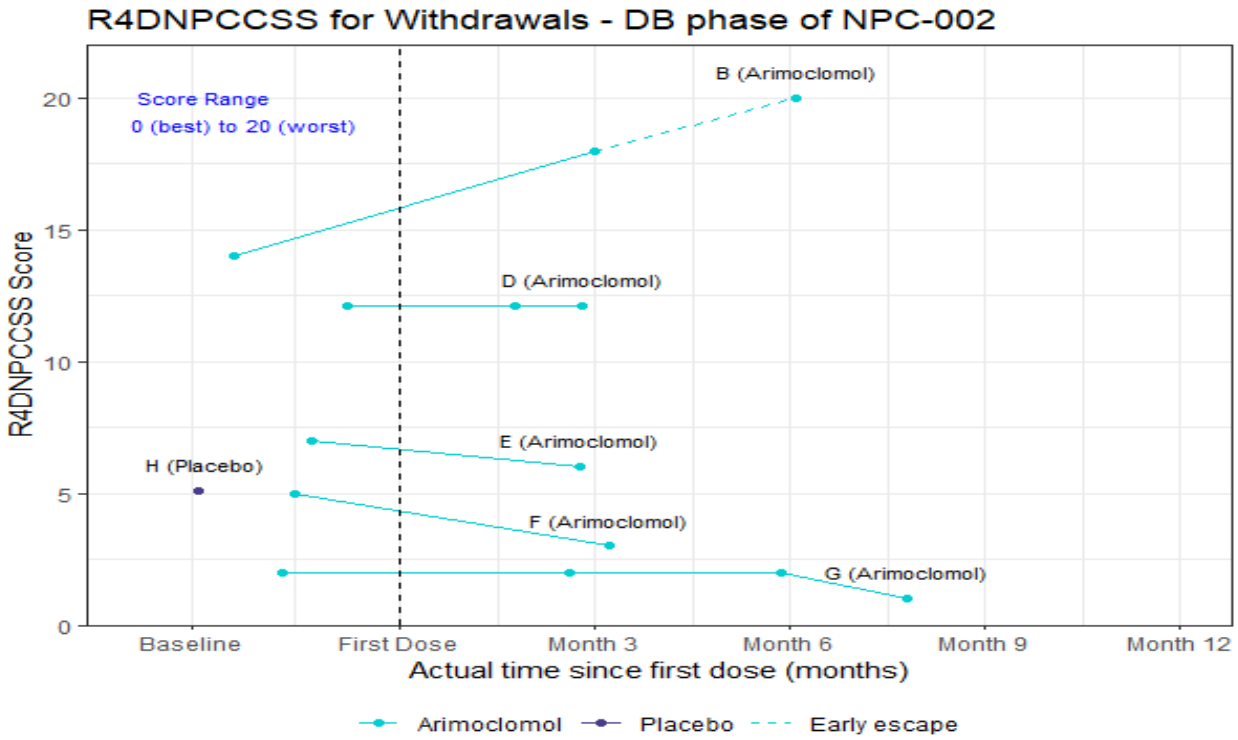
Applicant's Proposal in Resubmission

- Use the rescored 4-domain NPCCSS (R4DNPCCSS) score as the primary efficacy outcome
  - Removal of cognition domain (as agreed with FDA)
  - Rescoring swallow domain
- **Use the post hoc primary efficacy endpoint: change in R4DNPCCSS score from baseline to the last visit while on treatment** (including open-label use after early escape)
  - This endpoint incorporates data after early escape and the worst observed score for the subject who died
  - ANCOVA model including baseline miglustat use and baseline R4DNPCCSS score (referred to as "while-on-treatment" strategy)

FDA's Post Hoc Analysis for Resubmission: Treatment Policy Strategy

- ANCOVA analysis of change in R4DNPCCSS score from baseline to month 12
- For the subject who died prior to month 12, outcome of this endpoint is defined as the worst change from baseline prior to death
- For the subjects who prematurely discontinued the study prior to month 12, R4DNPCCSS outcome is considered missing and explicitly imputed

Missing Data



R4DNPCCSS scores at month 12 are missing for 6 subjects (5 in arimoclomol and 1 in placebo)

Source: FDA's figure

Missing Data Imputation Methods

Three missing data imputation methods:

- Method 1 uses the worst observed change within each subject
- Method 2 uses the maximum value between the worst observed change within each subject and **the median change at 12 months in the placebo group**
- Method 3 is a multiple imputation (MI) method. The MI method is implemented as follows:
  a) A random number is generated from **the observed distribution of change from baseline to 12 months in the placebo group**
  b) A total of 100 imputed datasets are created and results from the 100 imputed datasets are combined using the Rubin's rule
- All methods assume that the subject who reached the worst possible score of 20 remains the same after treatment discontinuation

Imputed Values for Missing Data

Subject	Arm	Change from baseline to last visit	Imputed change from baseline to Month 12		
			Method 1	Method 2	Method 3
B	Arimoclomol	6 (from 14 to 20)	6	6	6
D	Arimoclomol	0 (from 12 to 12)	0	1	1.96 (3.2)
E	Arimoclomol	-1 (from 7 to 6)	0	1	1.44 (2.5)
F	Arimoclomol	-2 (from 5 to 3)	0	1	1.98 (3.0)
G	Arimoclomol	-1 (from 2 to 1)	0	1	1.68 (2.9)
H	Placebo	0 (from 5 to 5)	0	1	2.11 (3.2)

Source: FDA's table. Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

For Method 3 (multiple imputation), the table presents mean (SD) among 100 imputed values within each subject.

Efficacy Results for Post Hoc Analyses of R4DNPCCSS

- Favors the arimoclomol arm: the point estimate of treatment difference ranges from -1.5 to -1.2 depending on the strategies of handling study discontinuation.

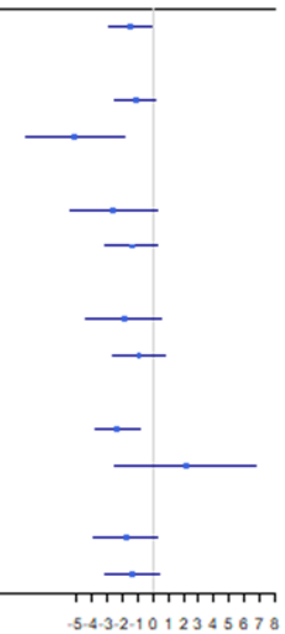
  Note: death and early escapes are handled in the same way in both while-on-treatment and treatment policy strategies

	Arimoclomol (N=34)	Placebo (N=16)	Difference (95% CI)
Baseline R4DNPCCSS, Mean (SD)	9.2 (5.8)	6.7 (5.2)	
Estimated Mean Change (SE)			
Hypothetical strategy			
Applicant's Prespecified MMRM	0.33 (0.40)	2.02 (0.54)	-1.70 (-3.05, -0.34)
Applicant's while-on-treatment strategy	0.62 (0.39)	2.12 (0.59)	-1.51 (-2.95, -0.06)
Agency's treatment-policy strategy			
Method 1 (worst change)	0.73 (0.39)	2.01 (0.57)	-1.29 (-2.68, 0.11)
Method 2 (placebo median)	0.85 (0.39)	2.06 (0.57)	-1.21 (-2.61, 0.20)
Method 3 (multiple imputation)	0.95 (0.46)	2.12 (0.66)	-1.17 (-2.76, 0.43)

Source: FDA's analyses. Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; MMRM, mixed model repeated measure; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SD, standard deviation; SE, standard error.

Subgroup Analysis for R4DNPCCSS

Subgroup	Arimoclomol N / Mean	Placebo N / Mean	Difference (95% CI)
Overall	34 / 0.62	15 / 2.13	-1.5 (-3.0, -0.1)
Age at baseline			
< 12 years	16 / 1.09	10 / 2.26	-1.2 (-2.5, 0.2)
>= 12 years	18 / -0.55	5 / 4.58	-5.1 (-8.3, -1.9)
Age at first neuro symptom			
< 2 years	6 / 0.02	3 / 2.63	-2.6 (-5.5, 0.3)
>= 2 years	28 / 0.70	12 / 2.11	-1.4 (-3.2, 0.3)
Sex			
Female	17 / 0.38	8 / 2.31	-1.9 (-4.4, 0.5)
Male	17 / 0.90	7 / 1.82	-0.9 (-2.7, 0.8)
On miglustat			
Yes	26 / -0.38	12 / 1.99	-2.4 (-3.8, -0.9)
No	8 / 4.13	3 / 1.98	2.2 (-2.5, 6.8)
Baseline score			
<= 8	17 / 0.19	11 / 1.98	-1.8 (-3.9, 0.3)
> 8	17 / 1.07	4 / 2.46	-1.4 (-3.2, 0.4)



Source: FDA's figure.

Summary of Efficacy in Study NPC-002

- The prespecified primary analysis result for the primary 5DNPCCSS endpoint in the original submission meets statistical significance (two-sided p-value < 0.05)
  - However, it has limitations due to exclusion of the data after early escape and the data at the last unscheduled visit for the subject who died in the arimoclomol arm
  - It is notable that the excluded data indicated disease worsening
- For the post hoc R4DNPCCSS endpoint in the resubmission, the post hoc analysis results numerically favor the arimoclomol arm
- While there is uncertainty regarding the estimated treatment effect for both 5DNPCCSS and R4DNPCCSS endpoints, the point estimates in the multiple analyses show slower progression in the arimoclomol arm compared to the placebo arm during the 12-month double-blind period. However, there are concerns regarding the validity of these endpoints

NPCCSS: Measurement Considerations

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Division of Clinical Outcome Assessment
Office of Drug Evaluation Science
CDER, FDA

Federal Rules and Regulations

- FDA has evidentiary standards under federal rules and regulations specifying that endpoints, the methods of assessment of patients' responses, are well-defined and reliable (CFR §314.126)
- Some of the evidence comprising "well-defined and reliable" falls into two broad categories:
  - validity
  - reliability
- Validity and reliability evidence are necessary to support score interpretation which is fundamental to understanding clinical trial results

Niemann Pick Disease Type C Clinical Severity Scale (NPCCSS)

- The NPCCSS was developed for retrospective and prospective patient monitoring
- The five-domain NPCCSS (5DNPCCSS) was used to measure cognition, ambulation, fine motor, speech, and swallow in study NPC-002
  - Following from foundational qualitative survey and interview research with patients, caregivers, and clinical experts

NPCCSS Complete Response Concerns

- Concerns from the initial review included the interpretability of the 5DNPCCSS, specifically the swallow and cognition domains
  - **Standardized administration of the NPCCSS**
  - **Speech, fine motor, ambulation:** In the resubmission, the Applicant provided additional correlational evidence
  - **Cognition:** For the resubmission, the Applicant and the Agency agreed to omit cognition, where ratings depended on the patient environment (e.g., access to support services)
  - **Swallow:** In the resubmission, the Applicant provided additional qualitative and quantitative evidence regarding the uncertainties raised regarding the swallow domain

Standardized Administration of the NPCCSS

- Standardized administration of a COA helps ensure that data are valid and reliable
  - The Applicant provided clinicians with an NPCCSS scoring manual as well as a training and indicated that patients were rated by the same clinician when feasible; however, it is unclear which clinicians performed ratings and with which caregiver(s) at each visit for NPC-002
  - Qualitative interviews with clinicians indicated standard NPCCSS practice involves clinicians observing patients and asking the patient and/or caregiver for observations, with variability noted across clinicians about aspects of functioning queried and next steps taken

Given the specific trial setting and assessment, the Agency is interested in the panel's thoughts on the impact and/or potential lack of impact of the processes used to assess the endpoint in NPC-002.

Swallow Uncertainties and Applicant Evidence

- The Agency identified uncertainties with the swallow domain, specifically:
  - Comprehensiveness of the assessment of swallowing, including non-observable features (e.g., silent aspiration)
  - Overlapping response options
  - Appropriateness of response option ordering (i.e., by increasing disease severity)
- In response the Applicant:
  - Rescored the swallow domain, on which the Agency seeks AC advice
  - Conducted qualitative semi-structured interviews with NPC clinicians and swallow experts, which provided evidence that the scale was appropriately ordered by severity from the perspective of most clinical experts
  - Provided correlations with NIH study data; the Agency also conducted analyses with NIH study data

Remaining Swallow Domain Uncertainties

- The NPCCSS swallow domain measures observable features, but does not appear to measure non-observable aspects (e.g., aspiration without a protective airway reflex)
  - FDA's cross-sectional and longitudinal analyses with NIH data indicated differences in swallow scores across the PAS and ASHA-NOMS in the NPCCSS 0 to 3 range, indicating these scales measure different aspects of swallow, which was also concluded by the Applicant
- A clinical trial measurement approach that incorporated both observable and non-observable swallowing measurement, when indicated, would be consistent with NPC clinical management guidelines and offer a more comprehensive picture of swallowing function

Given these considerations, the Advisory Committee is asked to consider whether data from the R4DNPCCSS as implemented in NPC-002 can be interpreted to represent a sufficient assessment of swallow function in NPC and, if so, whether the R4DNPCCSS inclusive of the swallow domain constitutes a comprehensive assessment of neurological function in NPC.

ASHA-NOMS: American Speech-Language-Hearing Association National Outcomes Measurement System; PAS: Penetration Aspiration Scale

Arimoclomol
(NDA 214927)
Additional Data: Nonclinical
August 2, 2024

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Overview

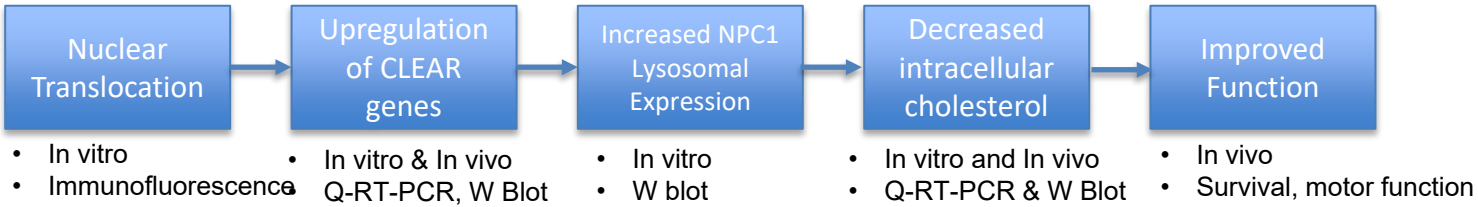
- Complete Response
- Proposed mechanism of action (MOA)
- In vitro data with arimoclomol with or without miglustat
- Data from NPC1$^{-/-}$ and NPC1$^{nmf/nmf}$ mice treated with arimoclomol and/or miglustat
- Conclusions

Complete Response

- In the Agency's Complete Response letter, the nonclinical data were described as weak and contradictory
- The Agency recommended additional in vitro, nonclinical and/or clinical data to support subgroup findings
- Resubmission contained
  - Studies in the NPC1$^{nmf/nmf}$ mouse
  - Studies characterizing effects on the Coordinated Lysosomal Expression and Regulation (CLEAR) network
  - Studies characterizing the MOA in wildtype (WT) and patient-derived fibroblasts

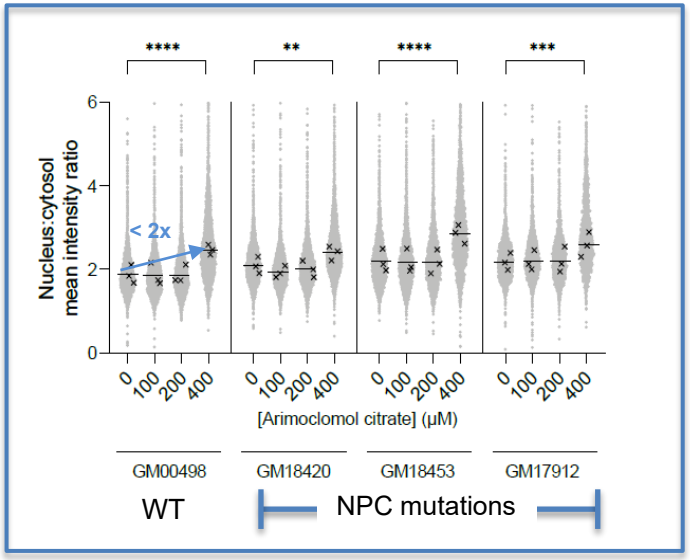
Proposed MOA

- The Applicant proposes that arimoclomol activates the CLEAR Network: Coordinated Lysosomal Expression and Regulation
  - The CLEAR Network is mediated by activation of the transcription factors, TFE3 and TFEB
  - TFE3 and TFEB are transcription factors that are involved in the adaptive response to cellular stress
  - Upon activation, they migrate to the nucleus and bind to gene promoters leading to increased mRNA expression

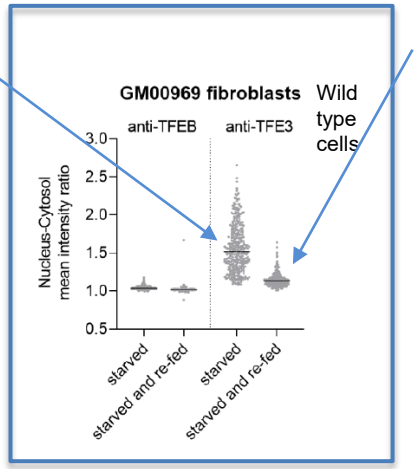


In Vitro Studies: TFE3/TFEB Nuclear Localization Similar Effects Seen in Starvation and Refeeding

Small increases in TFE3 nuclear localization seen at highest exposure only (30-60x the Clinical C_{max})



Starvation causes increased nuclear translocation



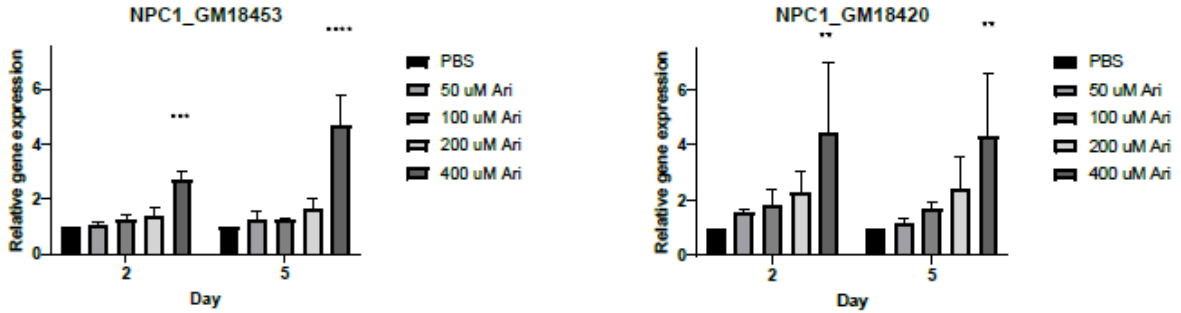
Reverses with refeeding

- *GM00969 and GM00498 are wildtype*
- *GM18453 (I1061T/I1061T) and GM17912 (P1009A/T1036M) are missense/missense*
- *GM18420 is missense/null (P1007A/Null)*

In Vitro Studies: NPC1 Expression

- Gene expression by rtPCR after 2-5 days of treatment
  - Cell lines were I1061T/I1061T (GM18453) and P1007A/gIVS23.4delA (GM18420)
- Small effects only at 60x Clinical C_{max}
- Cannot differentiate effect from toxicity

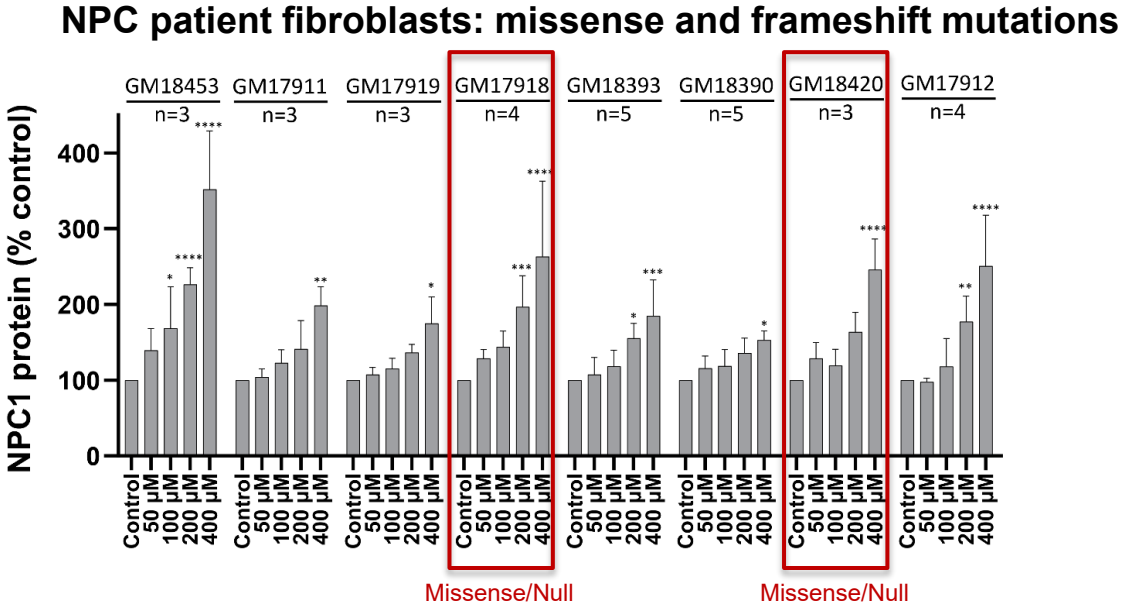
Effects of arimoclomol on two representative gene expression results in cell lines with NPC mutations*



*Similar responses seen on other CLEAR network genes

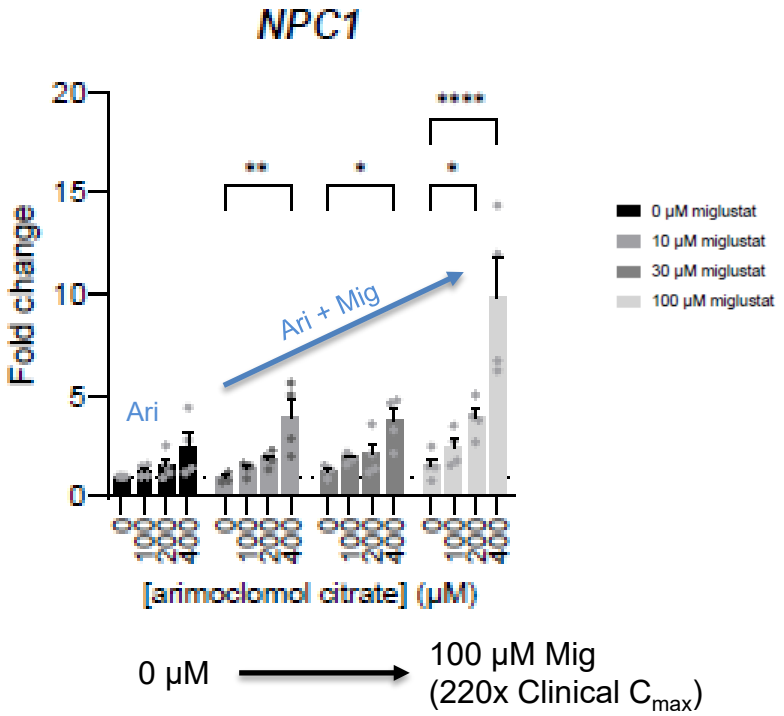
In Vitro Studies: NPC1 Protein Expression

- WT and NPC fibroblasts cultured for 5 days with arimoclomol
- Modest NPC1 protein upregulation with dose response
- No clear effect of genotype
- Effects significant at 30-60x Clinical C_{max}
- Viability data not provided



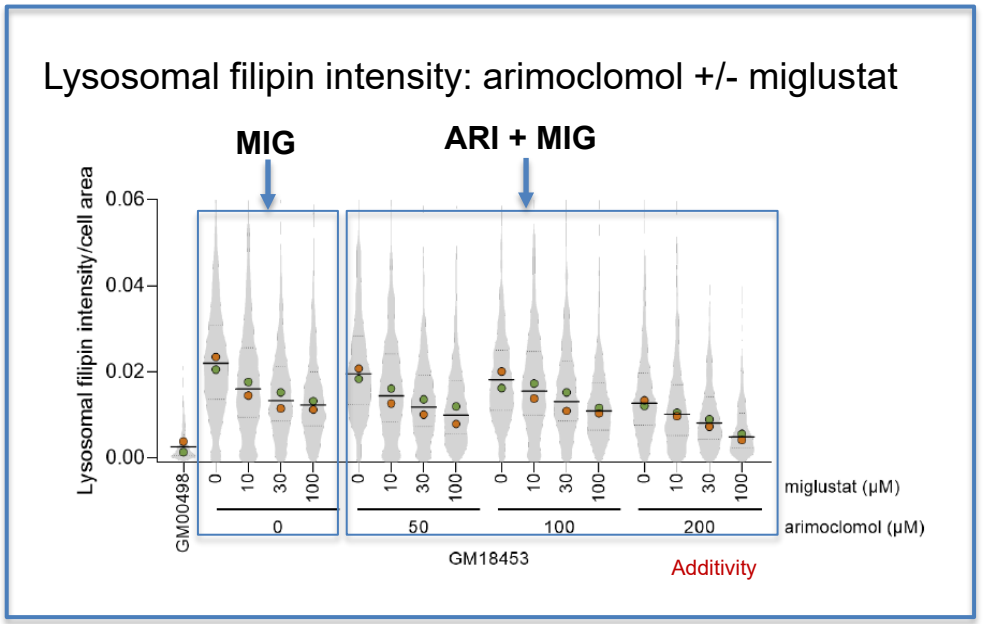
Arimoclomol ± Miglustat: CLEAR Gene Expression in NPC Cells

- Tested combination effects on CLEAR genes in cultured cells
  - Cell Line evaluated was GM18453 (I1061T/I1061T)
- Dose-responsive changes were noted
  - ARI: significant effects only at 60x clinical C_{max}
  - Combo: additivity for NPC1
- Effects on cellular health/viability were not assessed



Arimoclomol ± Miglustat: Cholesterol Levels

- Modest effect of Miglustat alone on filipin staining
- The combination appeared to show additivity
- Peak effects occurred at the highest concentrations of both drugs
- The effects increased with increasing durations of exposure
- Effects on cell viability or health not assessed



Summary: In Vitro Data

Arimoclomol induced:

- Small increases in TFE3 nuclear localization (similar to starved cell responses)
- Increased expression of CLEAR genes in NPC fibroblasts and NPC1 protein expression
- Reduced filipin staining – additive to miglustat

Limitations / issues:

- Responses seen at high drug concentrations (30-60 x clinical exposures) so of unclear translatability
- Cell viability not assessed – and responses can reflect cell stress responses

NPC Murine Models: Pathogenesis and Phenotypes

$NPC1^{-/-}$

- BALB/cNctr-$NPC1^{m1N}$/J:
  - Gene interruption model
- Develops an infantile-like form of NPC
- Mean life span is 9-11 weeks

$NPC1^{nmf/nmf}$

- C57BL/6J-$NPC1^{nmf164}$/J:
  - Chemically-induced point mutation
- Develops delayed onset and more slowly progressive form of NPC than $NPC1^{-/-}$
- Average lifespan is 112 days

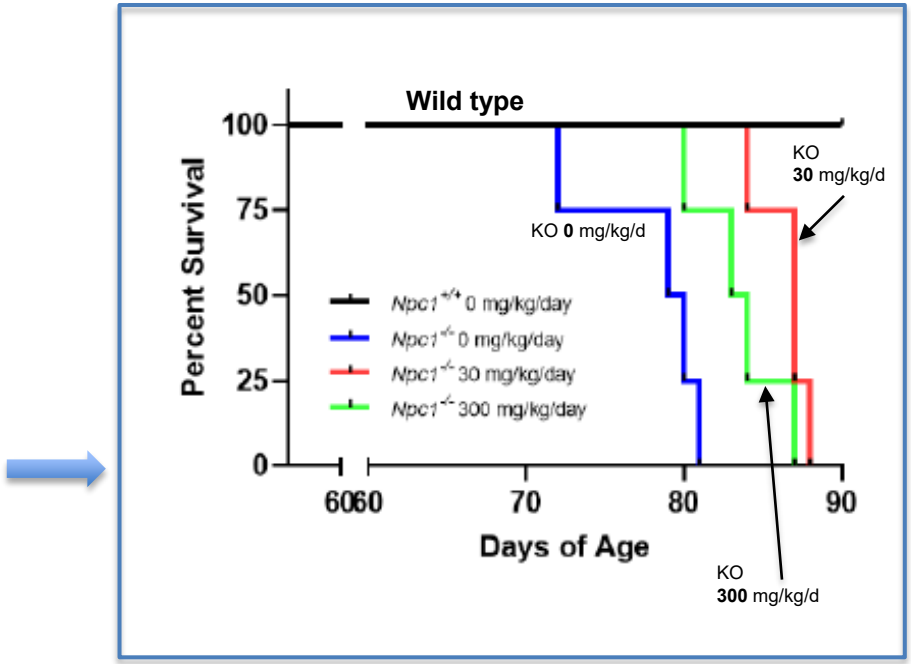
Study 13: Effects in NPC1$^{-/-}$ Mice: Survival & Motor Function

Study Design

- NPC1$^{-/-}$ are null for NPC1
- Initiated dosing at 3 weeks of age (pre-symptomatic)
- Doses: 0, 10, 30, 100, 300 mg/kg/day (4F/group)
- Drinking water/PK not evaluated

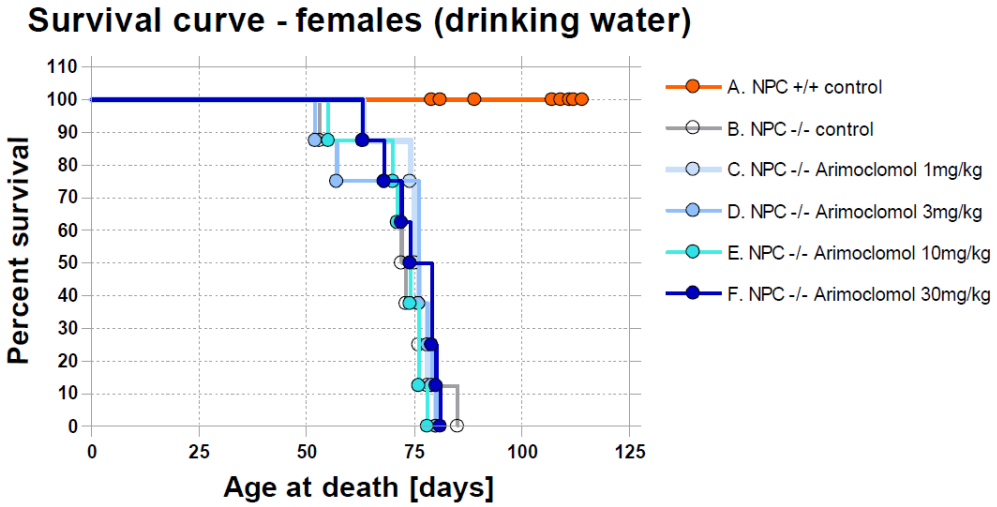
Results

- Modest increase (~8 days) in survival at 30 mg/kg/day; no response
- Mobility (gait, cadence, stance) effects were minimal, variable, and non-dose-related



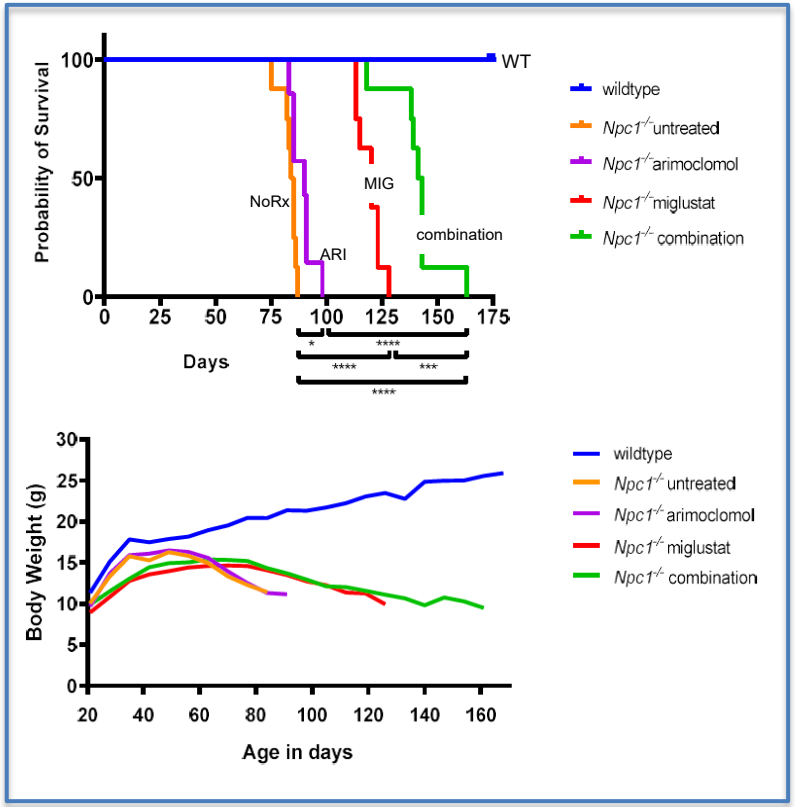
Study 53: Effects in NPC1$^{-/-}$ Mice: Survival & Motor Function

- Second Study in NPC1$^{-/-}$ mice
- Doses of 0, 1, 3, 10, and 30 mg/kg/day in the drinking water or 10 mg/kg BID by oral gavage.
- No effects on survival (including at 30 mg/kg/d)
- No other effects seen: behavior, motor function
- Biochemical analyses: no effects on liver cholesterol, or in liver or brain glycosphingolipids
- Water consumption was measured and found to be unaffected by drug



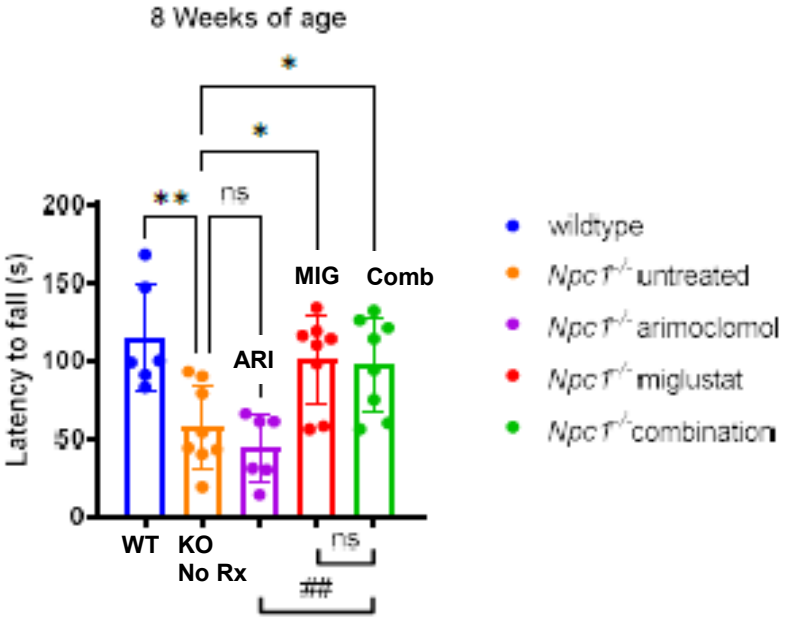
Study 43: Effects of Arimoclomol ± Miglustat in NPC1$^{-/-}$ Mice

- Ari doses (0, 30 mg/kg/day) administered in drinking water
- Mig doses (0 and 600 mg/kg/day) administered in feed
- Ari alone:
  - Modest effect on survival
- Mig and Ari + Mig improved survival
  - Effect of the combo appeared additive



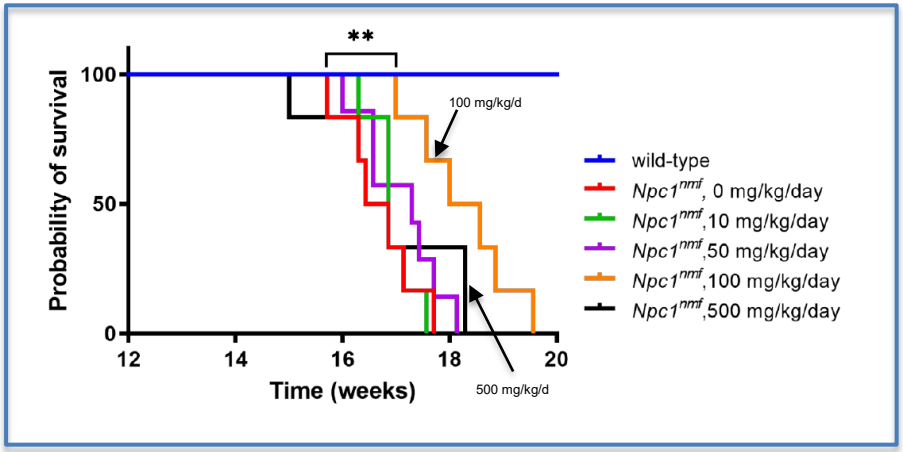
Study 43: Effects of Arimoclomol ± Miglustat on Motor Function in NPC1$^{-/-}$ Mice

- No effects of arimoclomol alone
  - Confirms results of Study 53, conducted at the same dose
- Transient improvement in latency to fall (figure) and distance traveled on the rotarod in miglustat and combination treated groups
  - No evidence of <u>greater</u> response for combination vs miglustat alone



Study 45: Effects in NPC1$^{nmf/nmf}$ Mice: Motor Function and Survival

- Doses evaluated were 0, 10, 50, 100, or 500 mg/kg of arimoclomol in drinking water
- Water consumption and PK were not evaluated
- Evaluated motor function, rearing, tremor, SHIRPA*and gait analysis and biochemical endpoints
- Results:
  - Small but significant increase in survival (~11 days) and BW at 100 mg/kg not seen at 500 mg/kg
  - Small effects on rearing and time spent rearing at lowest dose level at Week 17
  - No significant or numerically convincing effects on SHIRPA or gait analysis

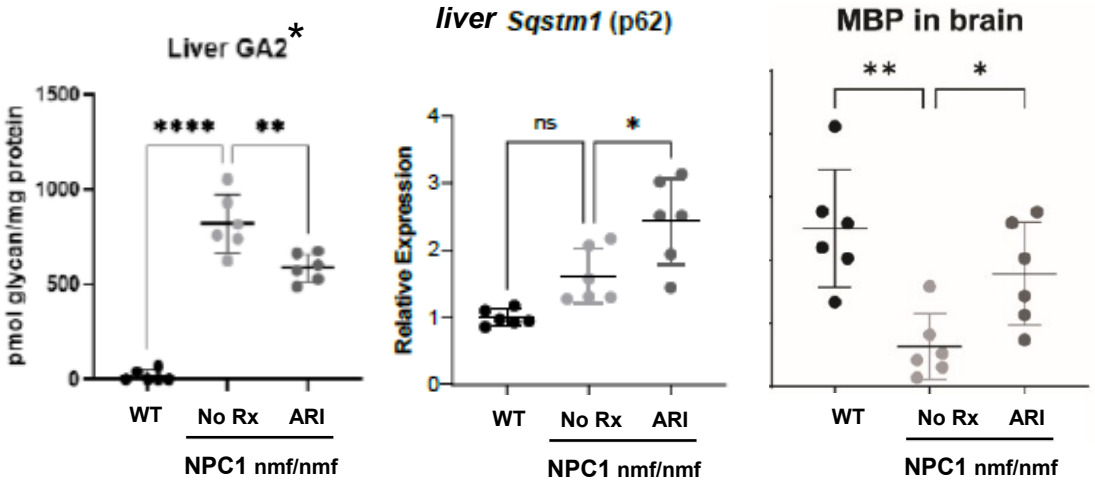


SHIRPA*: SmithKline Beecham Harwell Imperial College London Hospital phenotype assessment

Study 48: Effects in NPC1$^{nmf/nmf}$ Mice: Biochemical Endpoints

Liver and brain analyzed from 100 mg/kg animals

- Liver
  - ↓ glycolipid moieties
  - Only *Sqstm1* was upregulated
  - NPC1, HS1A1 and HSF1A1 - not upregulated
- Brain:
  - No effects on CLEAR network
  - Myelin basic protein was ↑ in the brain



***Similar effects of ARI seen for *liver* GM1, GM2gc, GM1b**

No significant response on *brain* CSLs: LacCer, GD1a, GM1, GM2, GM3, GT1b, GD1b, GA2, GM3gc, Gb3, and GlcCer

Conclusions (I)

- **In Vitro Studies**
  - Arimoclomol modestly increased CLEAR network genes and reduced filipin staining only at supraphysiological concentrations
  - Effects were indistinguishable from the effects of starvation
  - Effects on CLEAR gene expression and filipin staining were greater in cultured cells treated with arimoclomol + miglustat
- **In Vivo Studies**
  - Effects on survival and motor endpoints were small, variable, and lacked a dose-relationship and/or failed to repeat when re-tested
  - Effects on survival in NPC1$^{-/-}$ mice appeared be additive when tested in combination with miglustat
  - The Agency disagrees that a cross-study analysis was appropriate to analyze data across multiple animal studies (small number of animals, multiple labs, significant time between studies)
  - In both models, effects on biomarkers were suggestive of a weak effect on glycosphingolipids, particularly in the liver

Conclusions (II)

- **Limitations of the In Vivo Studies:**
  - Study designs were not robust and there were significant limitations: low N, uncertainty about randomization, criteria for humane endpoints, etc.
  - Doses were administered in drinking water, and palatability was not evaluated at concentrations needed to deliver the full range of doses
  - Applicant did not measure plasma PK; so, it is unclear whether the nonlinear dose responses were due to failure to deliver the dose or secondary to toxicity
- **Overall:**
  - The nonclinical data provided limited support for arimoclomol effects.
  - Arimoclomol + miglustat combination may show improved survival or motor function; however, effects are difficult to differentiate from effects of miglustat alone

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Arimoclomol
Additional Data: Clinical Pharmacology
August 2, 2024

Sydney Stern, Ph.D.
Pharmacokineticist
Division of Translational and Precision Medicine (DTPM)
Office of Clinical Pharmacology
Office of Translational Sciences

Outline

- Background on biomarkers
- Biomarker results from NPC-002 double blind phase and open label extension in original NDA and re-submission
- Exposure-response relationship

Pharmacodynamic (PD) Biomarkers in NDA Submission

- Unesterified cholesterol
  - Accumulates as a result of aberrant cholesterol trafficking
- Cholestane-triol (c-triol)
  - Cholesterol derivative that indicates excess hepatic cholesterol and oxidative stress
- Lyso-SM-509 (*PPCS*)
  - Novel lipid elevated in patients with NPC
- Heat Shock Protein 70 (HSP70)
  - Target engagement for proposed arimoclomol mechanism
- Limitations:
  - Non-specific
  - Biomarker relationship to disease severity and progression
  - Whether blood biomarker concentrations reflects target tissue

Initial NDA Proposed Biomarkers as Confirmatory Evidence

- In the initial submission, the applicant proposed HSP70, unesterified cholesterol, c-triol, and lyso-SM-509 as confirmatory evidence for arimoclomol in NPC-002
  - No significant change from baseline to Month 12 between arimoclomol-treated patients and placebo-treated for any of the PD biomarkers

- FDA recommended a short-term, cross-over pharmacodynamic study using sufficient validated assays in reasonable number of patients to clearly establish arimoclomol's effects on biomarkers related to its mechanism in NPC
  - In the NDA re-submission, biomarkers are no longer proposed to serve as confirmatory evidence

Pharmacodynamic Biomarkers Summary

The PD biomarker data showed:

- No difference in the 4 biomarkers at any timepoint
- No consistent trends in increases over the double-blind or 60-month period
- missing data

Limitations:

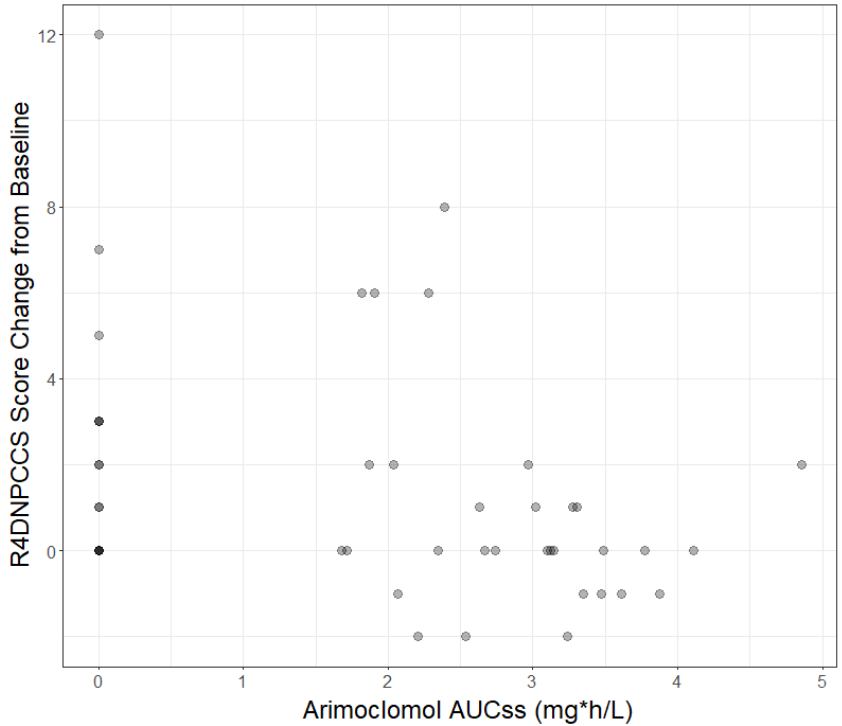
- low sample acquisition
  - Only 50-60% of the placebo- and arimoclomol-treated group had samples collected at both baseline and Month 12
- high inter-subject and intra-subject variability

Therefore, the available PD biomarker data does not serve as confirmatory evidence for arimoclomol in study NPC-002; however, because of the limitations outlined above we also cannot conclude an absence of a pharmacological effect of arimoclomol

Exposure-Response Analysis for Efficacy

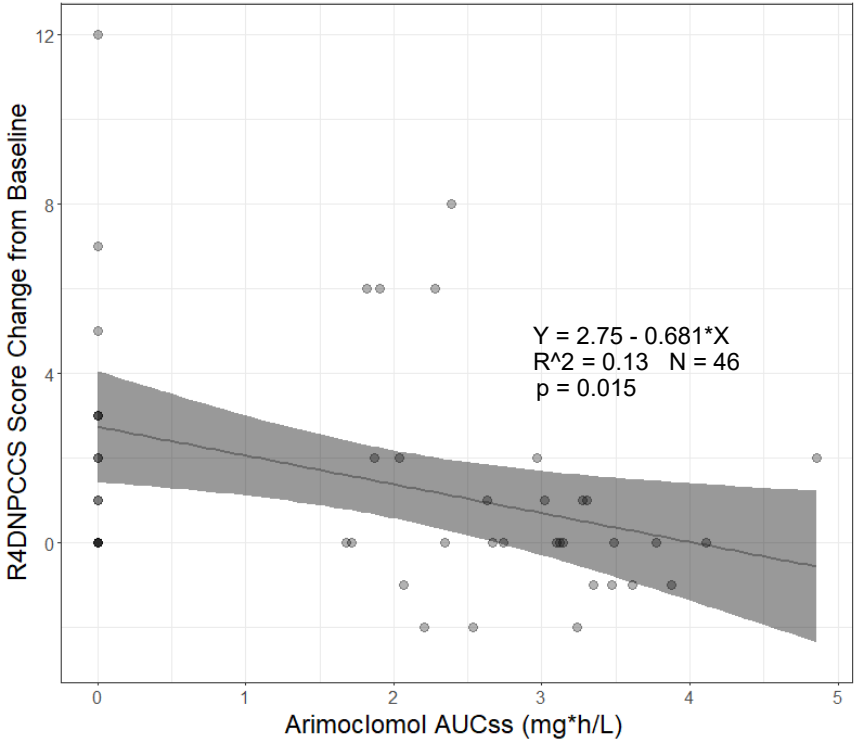
- Exposure: AUC_{ss} is the area under the plasma arimoclomol concentration-time curve over a dosing interval at steady-state
- Response: change in R4DNPCCSS from Baseline vs Last visit while on treatment in Study NPC-002
- Majority of patients were receiving miglustat
- The E-R analysis is exploratory and for trend illustration

Exposure-Response Analysis for Efficacy



Source: FDA Pharmacometrics reviewer's analysis using data from NPC-002. Note that 3 patients with missing PK data were excluded in the analysis.

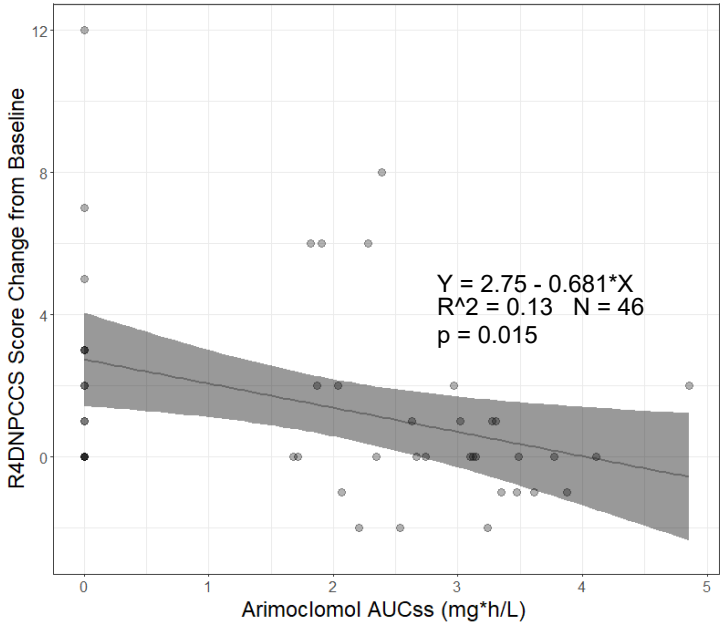
Exposure-Response Analysis for Efficacy



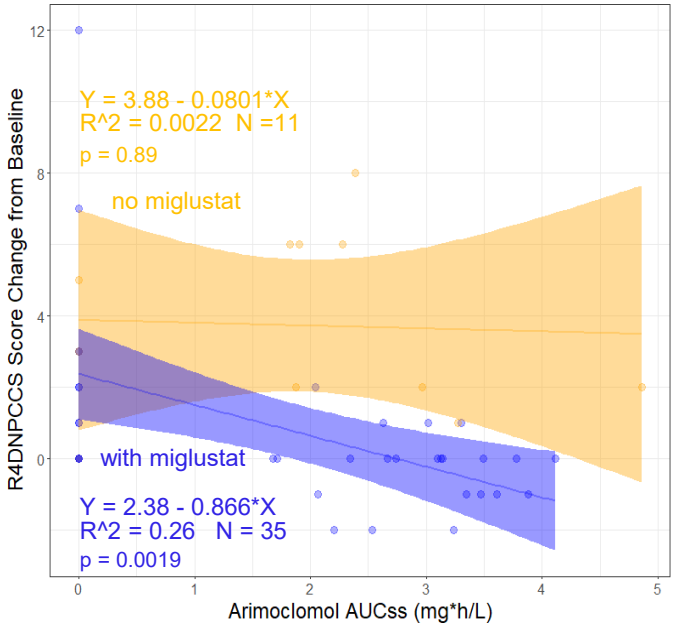
Higher exposure of arimoclomol is associated with a greater reduction in R4DNPCCSS.

Source: FDA Pharmacometrics reviewer's analysis using data from NPC-002. Note that 3 patients with missing PK data were excluded in the analysis.

Exposure-Response Analysis for Efficacy



Subgroup Analysis by Miglustat use



Source: FDA Pharmacometrics reviewer's analysis using data from NPC-002. Note that 3 patients with missing PK data were excluded in the analysis.

Summary of Key Points

- The PD biomarker data presented in the original NDA submission and the NDA resubmission exhibit the same limitations associated with missing data, low sample acquisition, and high inter/intra-subject variabilities
- The available PD biomarker data does not serve as confirmatory evidence for arimoclomol in study NPC-002; we also cannot conclude an absence of a pharmacological effect of arimoclomol
- Arimoclomol's mechanism of action is unclear and HSP70 is unchanged by treatment
- The role of these biomarkers in disease progression and their correlation with NPC clinical presentation remain unknown
- Systemic concentrations or changes to these biomarkers may not reflect CSF concentrations
- The E-R relationship for efficacy alone is not considered adequate as CE due to limitations of the data, despite that a trend in the E-R relationship has been identified which potentially supports the activity of arimoclomol

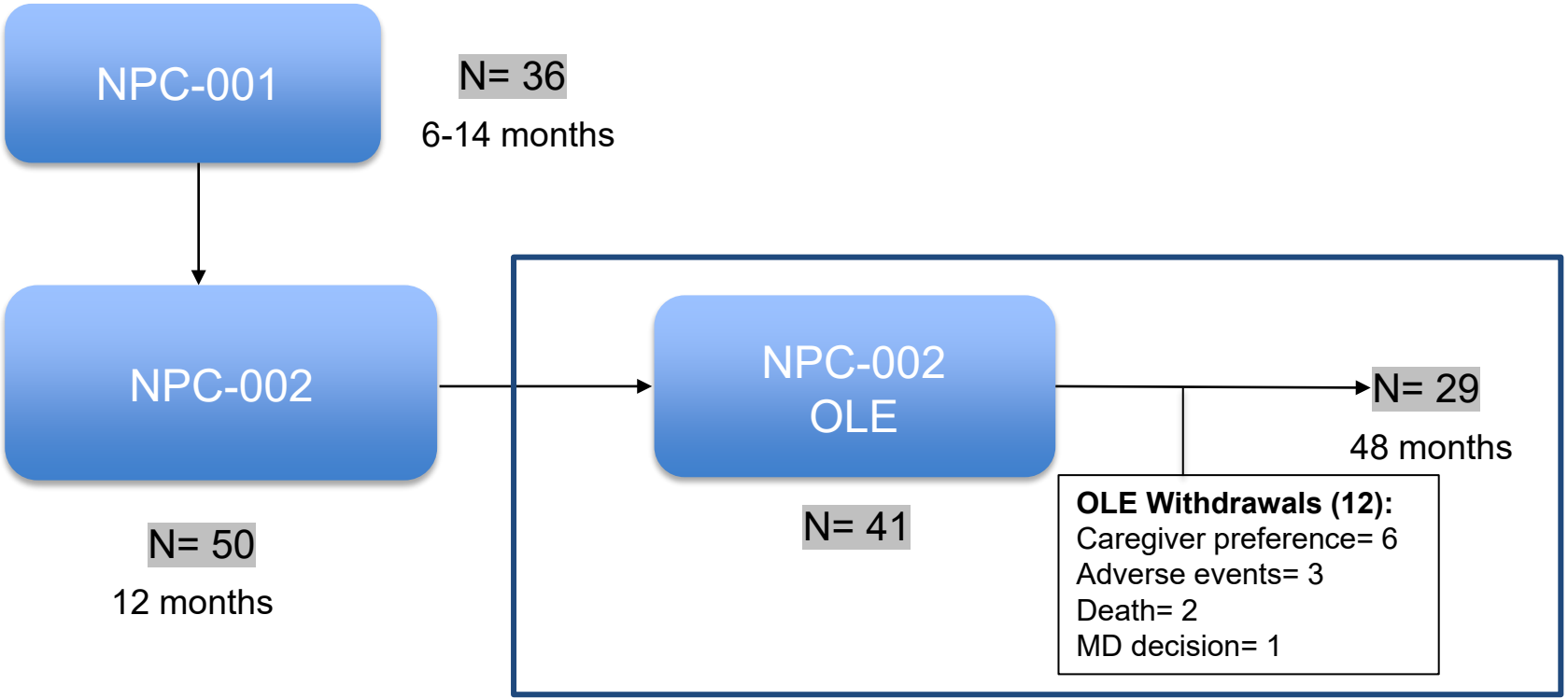
Additional Clinical Data and Summary

Maura RZ Ruzhnikov, MD, FACMG
Clinical Reviewer
Division Of Rare Diseases And Medical Genetics

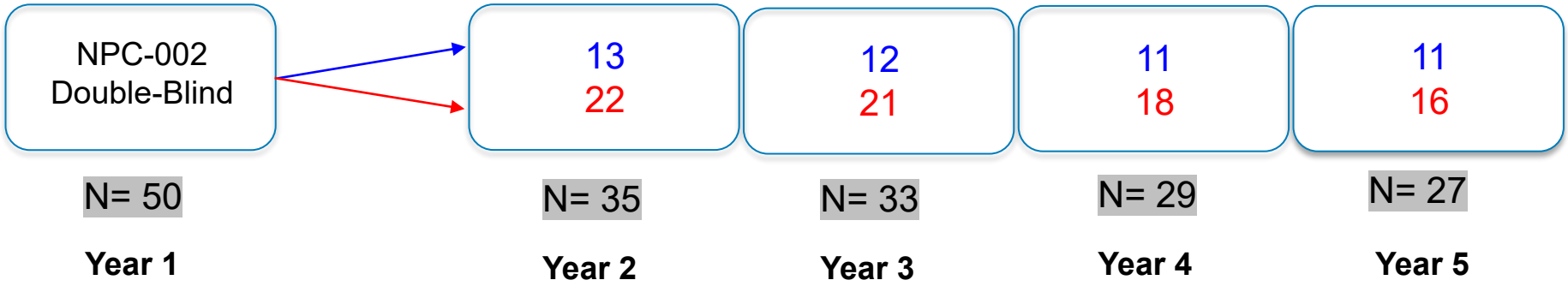
Clinical Data Sources

- Open-label extension of study NPC-002 (NPC-002 OLE)
- Comparison of NPC-002 OLE to natural history data from the National Institutes of Health (NIH NHS)
- Observational study NPC-001
- Data from patients treated with arimoclomol under expanded access protocols

NPC-002 OLE


NPC-001
N= 36
6-14 months
NPC-002
N= 50
12 months
NPC-002
OLE
N= 41
N= 29
48 months
OLE Withdrawals (12):
Caregiver preference= 6
Adverse events= 3
Death= 2
MD decision= 1

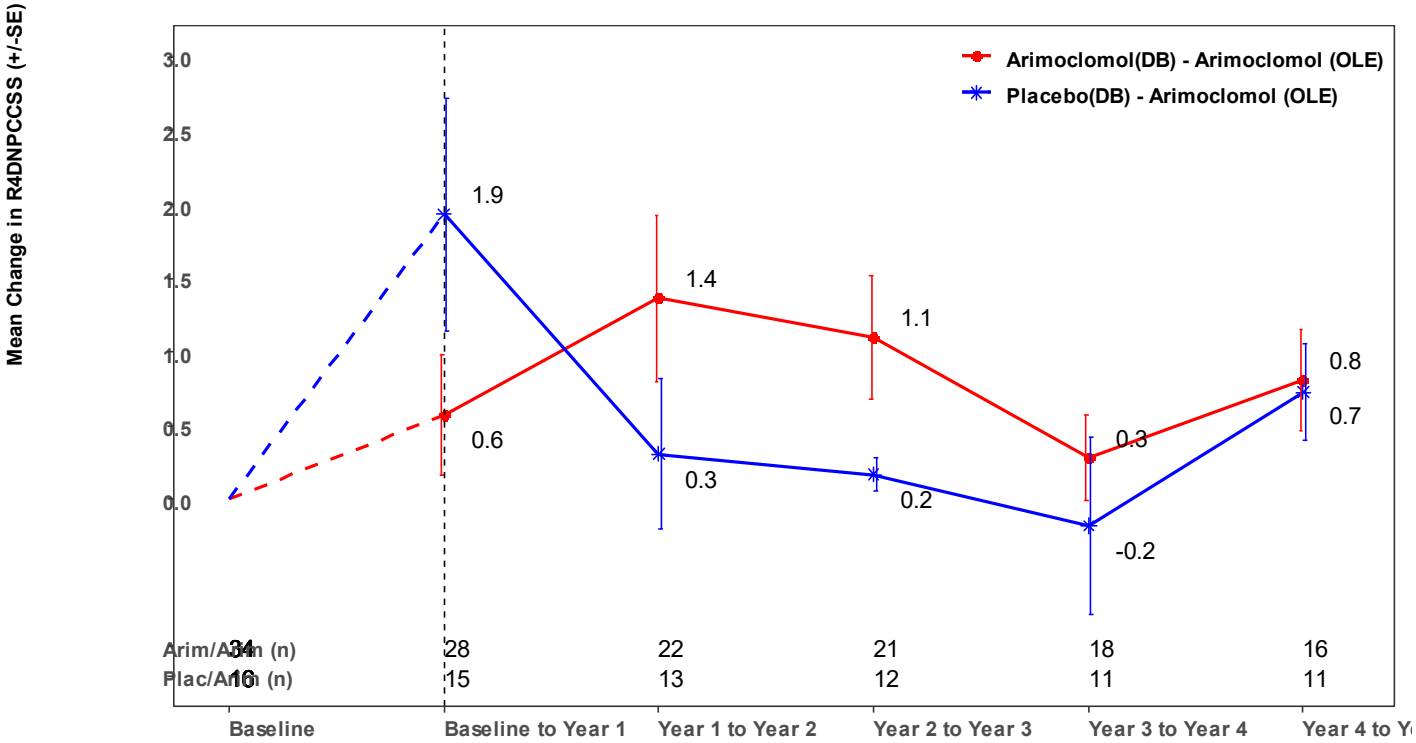
NPC-002 OLE



= placebo cohort

= arimoclomol cohort

Mean Year-to-Year Change in R4DNPCCS Scores (OLE)



Source: FDA's figure

Potential Drivers of Rapid Progression

- Clinical features examined as potential drivers of rapid disease progression:
  - Early symptom onset
  - High baseline 4DNPCCSS score
  - Not on miglustat
  - Double functional null mutations
- No single characteristic predicted a worse outcome

Summary of NPC-002 OLE Findings

- Lack of control group limits interpretability of the OLE
- Appears to show relative slowing/stability of disease progression with arimoclomol
- A subset of subjects progressed rapidly despite treatment with arimoclomol
  - Individual patient profiles highlight disease heterogeneity
  - No single disease characteristic predicted a worse outcome

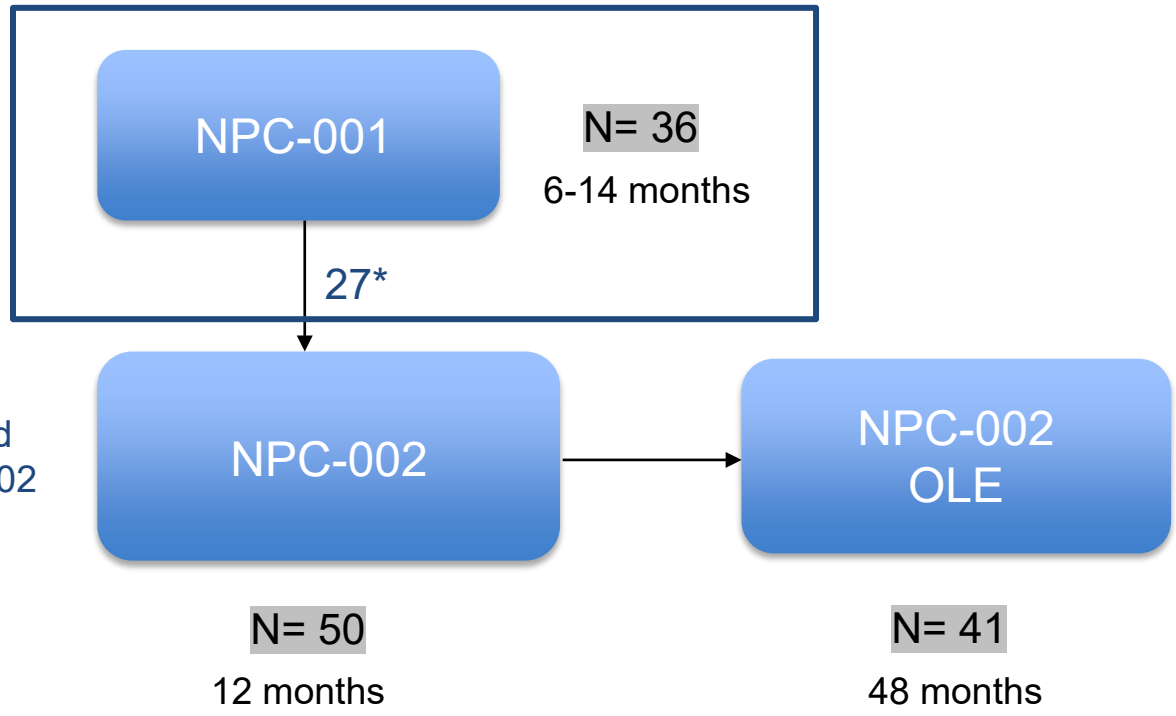
Comparison to NIH Natural History Study

- Ongoing NHS of NPC at NIH
- 23 NIH patients with at least 4 years of data
- Compared to 32 subjects from NPC-002 OLE
- Both case matching by strata and weighted approaches were analyzed
  - Variables: sex, miglustat use, baseline age, age at first neuro symptom, baseline 4DNPCCSS score
- Comparisons numerically favored arimoclomol, but did not approach statistical significance (p-values ranged 0.41-0.74)

Summary of Findings from NIH-NHS Comparison

- Post hoc comparison to NHS did not reach statistical significance
- Notable additional limitations include:
  - Very few subjects in NHS database for comparison
  - Baseline imbalance (NIH patients with milder baseline scores)
  - Initiation of off-label and other investigational products in NIH cohort (e.g., cyclodextrins)

Observational Study NPC-001



* 27 subjects who completed NPC-001 enrolled in NPC-002

Mean Change in R4DNPCCSS in Study NPC-001 Compared to NPC-002

Variable	Randomization in NPC-002		
	Arimoclomol	Placebo	Total
	(N = 18)	(N = 9)	(N = 27)
Change from baseline to end NPC-001			
Mean (SD)	**1.61 (2.97)**	**1.33 (1.66)**	1.52 (2.58)
Median (Min, Max)	1.0 (-3.0, 11.0)	0.0 (0.0, 4.0)	1.0 (-3.0, 11.0)
Change from baseline to end NPC-002			
Mean (SD)	**0.78 (2.53)**	**1.44 (1.33)**	1.00 (2.20)
Median (Min, Max)	0.0 (-2.0, 8.0)	1.0 (0.0, 3.0)	0.0 (-2.0, 8.0)

Summary of NPC-001 Comparison to NPC-002

- Appears to show slowing of disease progression with arimoclomol treatment
- Definitive conclusions regarding a treatment effect could not be drawn from this additional data on its own
  - Utilizes the same subjects as in the pivotal trial
  - Subjects serving as their own historical controls
  - Not a direct comparison of year-to-year change, NPC-001 had variable duration of 6-14 months
    - Median duration was 11.5 months for NPC-001 and was 12.3 months for NPC-002

Arimoclomol Expanded Access Programs (EAPs)

- Applicant submitted data from expanded access programs, a limited number of whom had at least two assessments within a similar timeframe
- EAPs focused on treatment (as opposed to clinical research)
- Notable limitations:
  - baseline imbalances
  - use of other and off-label therapies
  - variable assessment timepoints
  - limited number with longitudinal assessments
- Conclusions regarding potential efficacy could not be made

Summary of Additional Clinical Evidence

- NPC-002 OLE suggests slowing or stabilization of disease progression for up to 4 years in some subjects; a subset had rapid disease progression while on treatment
  - Uncertainty in the absence of an adequate control group
- Subjects who completed NPC-001 and randomized to arimoclomol in NPC-002 also showed slowing of disease progression after initiation of arimoclomol compared to placebo
  - Not a direct comparison of year-to-year change, relies on NPC-002
- Post hoc comparison to NIH NHS and EAP data have significant limitations

Overall Summary and Key Efficacy Issues

- NPC is a rare, serious disorder with unmet need for treatments
- NPC-002 study (pivotal trial) suggests slowing of disease progression
  - Concerns with the primary endpoint decreases the persuasiveness of the results of the single adequate and well controlled trial
- Additional clinical and nonclinical data to support the effectiveness of arimoclomol are limited

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Charge to the Committee

NDA 214927 Arimoclomol for the Treatment of Adult and Pediatric Patients 2 Years of Age and Older with Niemann-Pick Disease, Type C

Genetic Metabolic Diseases Advisory Committee (GeMDAC)
August 2, 2024

Arimoclomol: Proposed for Treatment of NPC

- NPC
  - A rare, serious disorder with devastating outcomes
  - Unmet need for effective therapy
- Arimoclomol
  - New molecular entity
  - Mechanism of action (MOA) is not fully elucidated

Overall Summary and Key Efficacy Issues

- NPC is a rare, serious disorder with unmet need for treatments
- NPC-002 study (pivotal trial) suggests slowing of disease progression
  - Concerns with the primary endpoint adds uncertainty to the persuasiveness of results of the single adequate and well controlled trial
- Additional clinical and nonclinical data to support the effectiveness of arimoclomol are limited

Regulatory Framework

- Substantial Evidence of Effectiveness
  - FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA has determined that such data are sufficient to establish effectiveness
  - FDA exercises flexibility within this regulatory framework

Discussion Question #1

- Discuss your assessment of the efficacy results of trial NPC-002. In your discussion, please comment on:
  - The 5-domain Niemann-Pick disease type C Clinical Severity Scale (5DNPCCSS) and the rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCCSS).
  - Your assessment of whether the trial results demonstrate a treatment effect of arimoclomol on the treatment of Niemann-Pick disease type C (NPC).

Discussion Question #2

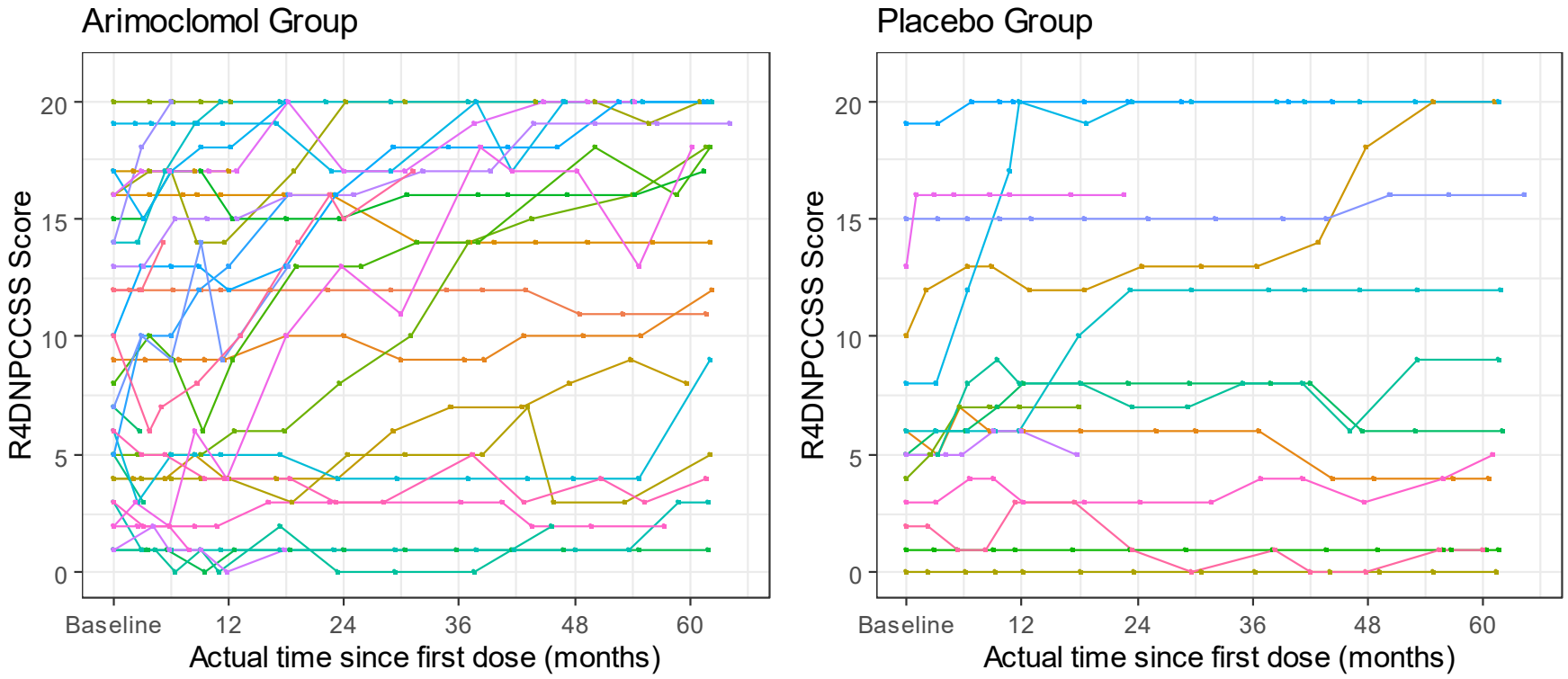
Discuss your assessment of other data (specifically the additional clinical and nonclinical data) with respect to support for the effectiveness of arimoclomol.

Voting Question

- Do the results of trial NPC-002 in concert with the other data (clinical and nonclinical in particular) support a conclusion that arimoclomol is effective in the treatment of patients with NPC? Provide a rationale for your vote.
  - If you voted no, provide recommendations for additional data that may support a conclusion that arimoclomol is effective.

Backup Slides

Individual R4DNPCCSS Profiles



Source: FDA's figure
Note: Higher scores indicate worse outcomes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