FDA Briefing Document

NDA 214927

Drug name: Arimoclomol

Applicant: Zevra Therapeutics

Genetic Metabolic Diseases (GeMDAC) Advisory Committee Meeting

August 2, 2024

Division of Rare Diseases and Medical Genetics

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought arimoclomol capsules, submitted by Zevra Denmark A/S, for the treatment of adults and pediatric patients 2 years of age and older with Niemann-Pick disease, Type C (NPC), to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
ANCOVA	analysis of covariance
CLEAR	coordinated lysosomal expression and regulation
COA	clinical outcome assessment
DB	double-blind
EL-PFDD	Externally Led Patient-Focused Drug Development
FDA	Food and Drug Administration
GD	Gaucher disease
GI	gastrointestinal
HSP	heat shock protein
KO	knockout
MAR	missing-At-random
MMRM	mixed model for repeated measures
MOA	mechanism of action
NDA	new drug application
NIH	National Institutes of Health
NPC	Niemann-Pick disease type C
NPCCSS	Niemann-Pick disease type C Clinical Severity Scale
OLE	open-label extension
PD	pharmacodynamic
SAP	Statistical Analysis Plan
SARA	scale for assessment and rating of ataxia
SHIRPA	SmithKline Beecham, Harwell, Imperial College, Royal London Hospital, Phenotype Assessment
TFEB	Transcription Factor EB
VFSS	videofluoroscopic swallow study
VoP	Voice of the Patient Report
WT	wildtype

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee meeting to discuss salient issues in the resubmission of the new drug application (NDA) for arimoclomol for Niemann-Pick disease type C (NPC) and to consider whether the Applicant has adequately addressed the deficiencies outlined by the FDA in the Complete Response to the original submission. In particular, the Agency requests that the committee examine the uncertainties regarding the four domain Niemann-Pick disease type C Clinical Severity Scale (4DNPCCSS) endpoint (the post hoc revision of the primary endpoint in the pivotal trial), and whether we can determine if there is a treatment benefit from arimoclomol based on the data from the pivotal trial, as well as to consider whether the additional clinical and nonclinical evidence provided supports the efficacy of arimoclomol for NPC.

1.2 Context for Issues to Be Discussed at the AC

Disease Background

NPC is a rare, life-limiting, devastating disease with profound impacts on patients and families and a significant unmet therapeutic need. NPC is a neurovisceral disorder caused by bi-allelic mutations in *NPC1* (95%) or *NPC2* (5%) (Patterson 2000). These mutations result in impaired intracellular trafficking and accumulation of unesterified cholesterol and glycosphingolipids within late endosomes and lysosomes. This lipid accumulation is cytotoxic and results in neurodegeneration as well as cellular degeneration in other tissues (e.g., hepatic, pulmonary). NPC is always progressive, but the primary manifestations, severity, and rate of progression are variable and typically categorized as perinatal or early infantile (0 to 2 years), late infantile (2 to 6 years), juvenile (6 to 15 years), and adolescent- or adult-onset phenotypes (>15 years) (Patterson 2000). The primary manifestations of NPC with symptom onset after 2 years of age are neurological with progressive decline in ambulation, fine motor skills, speech, swallowing and cognition; ultimately progressing to respiratory failure and death (te Vruchte et al. 2014). The reported median age of death for all of the phenotypes combined is 13 years (range 0.1 to 69 years), typically due to aspiration and/or respiratory failure (Bianconi et al. 2019).

There are no FDA-approved treatments for NPC. The current standard of care is primarily supportive, however the substrate reducing therapy miglustat (Zavesca) is approved in the European Union (EU), Canada, and Japan for the treatment of NPC. In the United States, miglustat is FDA approved for adults with Gaucher disease when enzyme replacement is not a therapeutic option. Off-label use of miglustat is considered the standard of care amongst treating clinicians in the US and is recommended according to international management guidelines for NPC (Geberhiwot et al. 2018).

Arimoclomol is an orally available small molecule that crosses the blood brain barrier. The mechanism of action (MOA) has yet to be fully elucidated, however, the Applicant asserts that converging evidence indicates that arimoclomol targets several biochemical pathways implicated in NPC. Primarily, the Applicant proposes that arimoclomol increases the transcription of several genes involved in lysosomal function and the proper folding and maturation of certain mutant NPC proteins, thus improving the impaired lipid trafficking and decreasing the lipid accumulation that ultimately causes disease symptoms.

1.3 Brief Description of Issues for Discussion at the AC

NDA 214927 for arimoclomol was originally submitted on July 17, 2020, and received a Complete Response on June 17, 2021.

A drug's effectiveness must be established by substantial evidence. FDA has generally interpreted this as a requirement for two adequate and well-controlled clinical investigations to establish effectiveness. However, 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 (see the guidance for industry, *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)). This approach is often used in development programs when it is not feasible or practicable to conduct more than a single adequate and well-controlled trial. When using one adequate and well-controlled trial, this approach must consider the availability and robustness of the available confirmatory evidence. In this NDA, the Applicant proposed such an approach for establishing substantial evidence of effectiveness. The single adequate and well-controlled clinical trial used to support this NDA was a 12-month, randomized, double-blind, placebo-controlled trial (Study CT-ORZY-NPC-002, henceforth referred to as Study NPC-002). Most subjects (78%) in this trial were receiving concomitant miglustat therapy. The proposed confirmatory evidence was comprised of 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), which assesses five clinical outcomes identified as meaningful to patients, caregivers, and clinical experts in NPC: swallowing, speech, fine motor, ambulatory, and cognitive functioning (EL-PFDD VoP 2019; Patterson et al. 2021). After thorough review, the Agency determined that the application could not be approved in its original form. Thus, a Complete Response letter was issued and the deficiencies cited were as follows:

- Concerns with the interpretability of the 5DNPCCSS (validity and reliability), particularly with regards to the swallow and cognition domains
- Concerns with the prespecified primary analysis for the 5DNPCCSS endpoint and lack of statistical significance at the conventional level ($p<0.05$) in the FDA's post hoc analyses of the 5DNPCCSS endpoint
- Weak and contradictory confirmatory evidence of effectiveness (in particular, inconsistent results among mouse studies and inconsistent pharmacodynamic (PD) biomarker data)

For the full text of the Complete Response letter, refer to Section 5.1. In the Complete Response letter, the Applicant was asked to address whether the NPCCSS swallow scores and other domain scores could be improved by rescoring, the lack of alignment of the NPCCSS swallow scores with performance-based measures of swallowing in a National Institutes of Health (NIH) natural history study, and the potential direction of bias in each of the domain scores and the total 5DNPCCSS score. The Applicant was also asked to provide additional quantitative and qualitative evidence to support the interpretation and use of 5DNPCCSS scores and consider whether additional analyses or other data from Study NPC-002 could address the concerns. The Applicant was further asked to bolster the confirmatory evidence, with potential examples being a short-term crossover PD study using sufficiently validated assays to establish arimoclomol's effects on biomarkers related to its MOA in NPC, or additional data from Study NPC-002.

To address the deficiencies outlined in the Complete Response letter, the current Applicant has included in the NDA resubmission results from NPC-002, and for primary efficacy, has re-analyzed the NPCCSS

using the rescored 4-domain NPCCSS (R4DNPCCSS), having removed the cognition domain and rescored the swallow domain. The Applicant maintains that the prior validation work for the 5DNPCCSS supports validation of the R4DNPCCSS. The Applicant has also submitted their proposed confirmatory evidence from the Open-Label Extension (OLE) phase of NPC-002, data from expanded access use of arimoclomol and comparison to the rate of disease progressions from an ongoing natural history study of NPC at the NIH, and in vitro mechanistic data intended to support the MOA, as well as additional in vivo studies in two mice models.

1.4 Draft Points for Consideration

- Discuss your assessment of the efficacy results of the NPC-002 trial. In your discussion, consider:
  - The uncertainties regarding the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS), including whether the assessment of the swallow domain was an adequate assessment of swallow function.
  - The uncertainties regarding the estimated treatment effect.
- Discuss your assessment of other data (specifically the additional clinical and non-clinical data) with respect to support for the effectiveness of arimoclomol.
- Discuss your conclusion as to whether the clinical study results in concert with the other evidence (clinical and nonclinical in particular) support a conclusion that arimoclomol is effective.

2 Introduction and Background

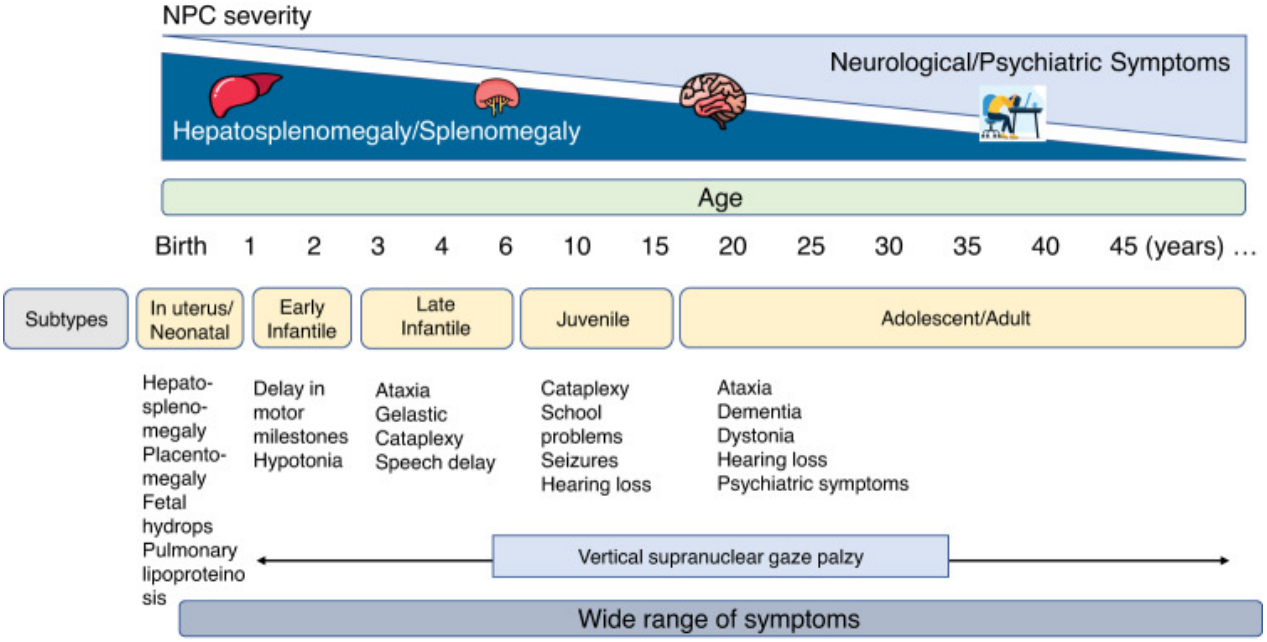
2.1 Background of the Condition/Standard of Clinical Care

NPC is an autosomal recessive lysosomal storage disorder caused by bi-allelic mutations in the genes *NPC1* (95%) and *NPC2* (5%) (Patterson 2000). NPC is a rare disease, with an estimated prevalence of one to three cases per million in the United States, although this is thought to be an underestimation given heterogeneity of the disease and likely missed diagnoses in milder phenotypes (Burton et al. 2021). Estimated incidences in different populations around the world have ranged from 1:90,000 to 1:120,000 live births (Wassif et al. 2016; Labrecque et al. 2021). NPC1 and NPC2 are important for late endo-lysosomal and lysosomal transport and metabolism of lipids including cholesterol. Their loss of function impedes cellular lipid trafficking and causes the accumulation of unesterified cholesterol, glucosylceramide, and gangliosides in the late endosomes and lysosomes of affected cells (although the precise mechanism by which this leads to neurodegeneration is unknown) (Tang et al. 2010). The accumulation of cholesterol and other lipids in peripheral tissues (mainly the liver and spleen) and in neurons and other non-neuronal cells in the central nervous system is thought to lead to the devastating and progressive neurovisceral symptoms that are the hallmarks of the disease.

NPC is always progressive, but the primary manifestations and prognosis are heterogenous, ranging from a rapidly progressive neonatal to a chronic neurodegenerative adult-onset disease course (Figure 1). NPC is typically categorized into age-dependent phenotypes, recognizing that they likely represent a continuum rather than distinct phenotypes. The four phenotypes described are 1) early infantile, with perinatal onset to 2 years of age, (2) late infantile, with onset from 2 to 6 years of age, (3) juvenile, with onset from 6 to 15 years of age, and (4) adolescent/adult, with onset after 15 years of age. The early infantile presentation is predominantly visceral with hepatosplenomegaly, jaundice, and pulmonary disease although some also have neurological symptoms (Seker Yilmaz et al. 2020).

Individuals with early infantile onset tend to have a rapidly progressive disease course progressing to death in early childhood. The late infantile and juvenile presentations are predominantly neurological with progressive decline in previously attained cognitive, gross and fine motor skills as well as progressive dysarthria and dysphagia. Additional neurological symptoms include ataxia, cataplexy, vertical supranuclear gaze palsy and epilepsy. Adolescent and adult onset of disease can be more insidious with cognitive and behavioral changes or other psychiatric manifestations at the onset followed by chronic neurological decline (Las Heras et al. 2023).

Figure 1. Phenotypic Spectrum of NPC



Source: Image from Las Heras et al. (2023) as adopted from Vanier (2010)
Abbreviations: NPC, Niemann-Pick disease type C

Disease progression in the neurodegenerative forms of the disease (onset >2 years of age) most commonly impacts ambulation, fine motor skills, speech, swallowing, and cognition. However, even within the late infantile and juvenile subgroups, the rate of neurological symptom progression is variable, with individuals having slower and faster rates of progression as measured by NPC-specific clinical severity scales. Several natural history studies of NPC in the literature have found that once neurological symptoms begin, intrapatient severity scores (measured on the 17-domain NPC Clinical Severity Scale [NPCCSS]) tend to continue to progress at a similar rate for at least several years (Yanjanin et al. 2010; te Vruchte et al. 2014). While lifespan can vary from a few days (severe neonatal onset) to a few decades, the reported median age of death, most often from respiratory failure, is 13 years (range 0.1 to 69 years) (Bianconi et al. 2019). Genotype-phenotype correlations are limited as there are hundreds of known pathogenic variants, and many individuals with NPC have compound heterozygous mutations. Generally, homozygous loss of function variants are more likely to result in a severe early-infantile phenotype (Millat et al. 2001). There are several well-characterized diagnostic biomarkers of NPC, such as plasma oxysterols and lyso-sphinogolipids (Boenzi et al. 2021). However, there are no validated biomarkers or laboratory parameters that have been correlated with disease status over time.

Currently, there are no approved treatments for NPC in the United States. The current standard of care is primarily supportive and includes the treatment of epilepsy with antiseizure medications as well as interventions to support feeding, mobility, communication, and behavior. Miglustat (Zavesca) is an iminosugar that acts as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme in the synthesis of many glycosphingolipids (which accumulate in NPC). Miglustat is approved in the United States for adult patients with mild or moderate type 1 Gaucher disease (GD) when enzyme replacement therapy is not a therapeutic option. Miglustat has been approved for the treatment of the progressive neurological manifestations of NPC in pediatric and adult patients in Europe and a number of other countries outside of the United States. Miglustat is often prescribed "off-label" for patients with NPC in the United States and is considered standard of care by treating clinicians. It is recommended as a treatment for NPC in international management guidelines for NPC (Geberhiwot et al. 2018), however, there is some question about its efficacy in patients with early infantile onset of their disease or who already have very severe symptoms (Freihuber et al. 2023). Despite widespread use of miglustat, NPC remains progressive and there has been no significant change in survival for NPC patients over the last 20 years (Bianconi et al. 2019).

2.2 Pertinent Drug Development and Regulatory History

Arimoclomol (arimoclomol citrate/BRX-345) is a synthetic pyridine derivative that is not currently identified within a specific drug class. The product is a crystalline, white to off-white powder that is packaged in capsules in one of four dosages (47 mg, 62 mg, 93 mg, and 124 mg) and is proposed for administration orally or via feeding tube three times daily in patients ≥2 years of age. Arimoclomol is proposed to affect biochemical mechanisms such as activation of the transcription factors E3 (TFE3) and EB (TFEB), leading to nuclear translocation and enhanced binding of TFEB3 to target gene promoters including *NPC1, NPC2, HSPA1A* (encoding HSP70), and *GBA.* The Applicant proposes that arimoclomol prolongs activation of heat shock factors under stress conditions, thus upregulating gene transcription of heat shock proteins (HSPs) that normally support lysosomal function and integrity through HSP-mediated augmentation of acid sphingomyelinase activity, stabilization of lysosomal membranes, and protection from cell death (Kirkegaard et al. 2010).

The original NDA (214927) was submitted in July 2020 seeking traditional approval. The primary evidence of efficacy was findings on an abbreviated version of the NPCCSS, using the five domains most meaningful to patients and caregivers (the 5DNPCCSS). After thorough Agency review, a Complete Response letter was issued on June 17, 2021. The three main deficiencies cited in the Complete Response letter were:

- Concerns with the interpretability (validity and reliability) of the 5DNPCCSS, particularly with regards to the swallowing and cognition domains
- Concerns with the Applicant's prespecified primary analysis for the 5DNPCCSS endpoint and lack of statistical significance at the conventional ($p<0.05$) in FDA's post hoc analyses of the mean change from baseline in the 5DNPCCSS
- Weak and contradictory confirmatory evidence of effectiveness to support a true drug effect.
- In this context of uncertainty regarding the estimated treatment effect, concerns with the validity of the 5DNPCCSS, and limitations of the confirmatory evidence, FDA took a complete response action on the original NDA.

After the complete response action, via a series of meetings with the Applicant, the Agency:

- Agreed with the Applicant's proposal to remove the cognition domain from the 5-domain NPCCSS (5DNPCCSS), thereby creating a 4-domain NPCCSS (4DNPCCSS). This proposal was in response to the Agency noting that the cognition domain ratings relied on the patient environment (e.g., access to services) and may not be adequately evaluated within the 12-month trial by a severity scale.
- Did not agree with a proposal to re-score the swallowing domain citing lack of evidence, protocols, and supporting materials establishing how the scores were initially assigned. Submission of these supportive material as well as qualitative evidence from clinical experts was recommended.
- Reiterated the concerns about the reliability and validity of the primary endpoint.
- Provided recommendations regarding confirmatory evidence including that:
  - The Applicant submit new data, such as in vivo or PD data, to adequately address the deficiencies in their original NDA submission.
  - The Applicant submit full study reports of all nonclinical studies along with a meta-analysis of the totality of their available nonclinical confirmatory evidence. The Agency emphasized remaining concerns about uncertainties around the consistency of the survival benefit when arimoclomol was administered to $NPC1^{-/-}$ and NPC^{nmf164} animals. The $NPC1^{-/-}$ mouse model is an NPC1 null strain in which an 824 bp Mammalian-Apparent Long-terminal repeat Retrotransposon replaced a 703 bp sequence of wildtype (WT) DNA. The $NPC1^{nmf/nmf}$ strain contains an A→G transition at codon 1005 of the NPC1 gene, resulting in an amino acid substitution. This mutation is comparable to those commonly found in humans. The Agency also expressed that while the biochemical and molecular nonclinical data appeared to support a potential MOA, by themselves, they did not appear to be sufficient to serve as confirmatory evidence to support the relationship between administration of arimoclomol in patients with NPC and effects on a clinically meaningful endpoint.
  - The Applicant consider the Agency's questions about the interpretability of the clinical data from the OLE phase of Study NPC-002 and whether it could contribute to confirmatory evidence.
- Expressed tentative alignment from the statistical team with the proposed statistical analysis plan and recommended including analysis results using a treatment policy strategy for handling the intercurrent events of treatment discontinuation due to adverse events, lack of efficacy, or withdrawal of consent.

The Applicant submitted a Complete Response in December 2023 seeking traditional approval of arimoclomol based on the findings of study NPC-002 with a modified analysis of the primary endpoint as primary support for efficacy along with additional confirmatory evidence.

A summary of the key regulatory history prior to the original NDA submission in May 2020 is described in the Appendix in Table 22.

3 Summary of Issues for the AC

3.1 Efficacy Issues

The following key efficacy issues are to be discussed at the AC meeting:

- The validity of the rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCCSS), which was the post hoc exploratory revision of the primary efficacy endpoint in the randomized trial.

- Uncertainty regarding the estimated treatment effect on the mean change from baseline in the revised primary endpoint (R4DNPCCSS) in the resubmission.
- Adequacy of the additional clinical and nonclinical evidence to provide confirmatory evidence supporting the efficacy of arimoclomol.
- The strength of the overall evidence to support the efficacy of arimoclomol.

3.1.1 Sources of Data for Efficacy

The clinical studies and programs that provided sources of data for efficacy are summarized in Table 1.

Table 1. Clinical Sources of Data for Efficacy

Trial	Design	Subjects	Dosing Regimen, Duration	Primary Endpoints
NPC-001	Prospective, observational study	N=36 ≥2 years and ≤18 years 11 months of age	Non-interventional study, 6-14 months	NPCCSS (and modifications 5DNPCCS, 4DNPCCS, R4DNPCCSS)
NPC-002 (Pivotal trial)	Double-blind, placebo controlled with 2:1 randomization	N=50 ≥2 years and ≤18 years 11 months of age	93-372 mg/day divided TID, 52 weeks	Change from baseline in 5DNPCCSS (and modifications 4DNPCSS, R4DNPCSS)
NPC-002 (OLE)	Open label extension phase of NPC-002	N=41 ≥2 years and ≤18 years 11 months of age	93-372 mg/day divided TID, Up to 48 months	Change from baseline in 5DNPCCSS (and modifications 4DNPCSS, R4DNPCSS)
NIH NHS	Prospective Natural History Study	N=120 (for evaluation of swallow domain, enrollment is ongoing) Any age	NA, NPC study initiated in 2006 and ongoing with visits every 6 months to 1 year (variable)	Multiple, including NPCCSS, functional swallow evaluations
Expanded Access Program	Expanded Access Protocol	N=81 in the US	Visits scheduled every 6 months, variable	NPCCSS (and modifications 5DNPCCS, 4DNPCCS, R4DNPCCSS)

Source: Reviewer generated
Abbreviations: NIH NHS, National Institute of Health Natural History Study; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; 5DNPCCSS, 5-domain NPCCSS; N, number; NA, not applicable; OLE, open-label extension; R4DNPCCSS, rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale; TID, three times daily

The primary source of efficacy data is the single, adequate and well-controlled trial, NPC-002. NPC-002 is a 12-month, randomized, double-blind, placebo-controlled study in patients with NPC, aged 2 to 19 years. 50 subjects with NPC were randomized 2:1 to receive arimoclomol or placebo three times a day. Randomization was stratified by use of miglustat (yes/no). A total of 39 (78%) subjects used concomitant miglustat as part of routine clinical care. The mean age for the total cohort was 11.1 years and the majority were white (90%). Most subjects (92%) were enrolled outside the United States. Given the similarities in NPC clinical care practices in Europe and the United States, the foreign data are applicable to the United States population. Table 2 presents the baseline demographics.

Table 2. Baseline Demographics in NPC-002

Characteristic	Arimoclomol N=34	Placebo N=16	Total N=50
Age, years			
Mean (SD)	11.5 (5.4)	10.2 (4.1)	11.1 (5.0)
Median (min, max)	12.5 (2.0, 19.0)	10.5 (3.0, 16.0)	11.0 (2.0, 19.0)
Age at first neurological symptoms, years			
Mean (SD)	5.1 (3.4)	5.2 (3.9)	5.1 (3.5)
Median (min, max)	4.0 (0.0, 14.2)	3.2 (0.0, 14.2)	4.0 (0.0, 14.2)
Genotype, n (%)			
Double functional null	3 (8.8)	0 (0.0)	3 (6.0)
Double missense	16 (47.1)	11 (68.8)	27 (54.0)
Missense/functional null	15 (44.1)	5 (31.2)	20 (40.0)
On Miglustat Therapy, n (%)			
Yes	26 (76.5)	13 (81.2)	39 (78.0)
No	8 (23.5)	3 (18.8)	11 (22.0)
Sex, n (%)			
Female	17 (50.0)	9 (56.2)	26 (52.0)
Male	17 (50.0)	7 (43.8)	24 (48.0)
Race, n (%)			
White	32 (94.1)	13 (81.2)	45 (90.0)
Asian	1 (2.9)	1 (6.2)	2 (4.0)
Unknown	1 (2.9)	1 (6.2)	2 (4.0)
Other	0 (0.0)	1 (6.2)	1 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (5.9)	0 (0.0)	2 (4.0)
Not Hispanic or Latino	32 (94.1)	16 (100.0)	48 (96.0)
Country, n (%)			
Switzerland	1 (2.9)	1 (6.2)	2 (4.0)
Germany	6 (17.6)	3 (18.8)	9 (18.0)
Denmark	1 (2.9)	2 (12.5)	3 (6.0)
Spain	2 (5.9)	1 (6.2)	3 (6.0)
France	3 (8.8)	2 (12.5)	5 (10.0)
Great Britain	7 (20.6)	2 (12.5)	9 (18.0)
Italy	5 (14.7)	1 (6.2)	6 (12.0)
Poland	5 (14.7)	4 (25.0)	9 (18.0)
United States	4 (11.8)	0 (0.0)	4 (8.0)

Source: Table 2-9 and Table 2-10 of Summary of Clinical Efficacy in the original submission.
Abbreviation: N, number of subjects; NPC, Niemann-Pick disease type C; SD, standard deviation

The dosages being studied were 93 to 372 mg/day divided three times daily depending on patient weight. Subjects who completed study NPC-002 were eligible to continue treatment (or begin treatment if they had been randomized to placebo) in the OLE phase of study NPC-002. A total of 41 subjects with NPC were enrolled in the NPC-OLE study, which has a duration of up to 48 months, or 4 additional years, of arimoclomol treatment.

Data and analyses from the study NPC-002 OLE as well as NPC-001, an observational study for up to 14 months conducted by the Applicant prior to initiation of study NPC-002 were also provided as a component of their proposed clinical confirmatory evidence. Subject-level data from an ongoing natural history study of NPC being conducted at the NIH and an Expanded Access Program sponsored by the Applicant under IND 214927 were also submitted and reviewed.

3.1.2 Efficacy Summary

In this NDA, the Applicant proposes to meet the substantial evidence of effectiveness requirement with evidence from a single adequate and well-controlled clinical trial and confirmatory evidence. As described in the FDA draft guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) and the guidance on Demonstrating Substantial Evidence of Effectiveness (September 2023), FDA considers the approach of using a single adequate and well-controlled trial with confirmatory evidence to be most appropriate when it is not feasible or practicable to conduct more than a single adequate and well-controlled trial. When using one adequate and well-controlled trial, this approach must consider the availability and robustness of the available confirmatory evidence. The intent is to view the results from the single trial in the context of the evidence from the body of confirmatory evidence, to assess whether information from both sources support the conclusion that the drug is, in fact, effective.

The single adequate and well-controlled clinical trial used to support this NDA was Study NPC-002. The protocol-defined primary endpoint was change from baseline to month 12 in the 5-domain Niemann-Pick disease type C Clinical Severity Scale (5DNPCCSS), which assesses five clinical outcomes that are meaningful to patients: swallowing, speech, fine motor, ambulatory and cognitive functioning. In the prespecified primary analysis using a mixed model for repeated measures (MMRM), the estimated treatment difference was -1.4 (95% CI: -2.76, -0.03; p=0.0456), which met the conventional statistical significance (two-sided p-value<0.05). However, the prespecified MMRM analysis excluded the data collected after early escape for two patients and the data collected at the last visit for a patient who died, which can be impactful for estimation of a treatment difference (see Sections 3.1.3.2.1 and 3.1.3.2.2). In FDA's post hoc analyses including such data, the estimated treatment difference ranged from -1.2 to -0.9, which still numerically favored the arimoclomol arm but resulted in nominal p-values (0.12 to 0.30) above 0.05. In this context of uncertainty regarding the estimated treatment effect, FDA noted concerns with the validity of the 5DNPCCSS, specifically regarding both cognition and swallowing domains, and limitations of the confirmatory evidence. As a result, FDA took a complete response action on the original NDA.

In this resubmission, the Applicant proposes to use the post hoc exploratory R4DNPCCSS score as the primary efficacy outcome, which is obtained by removing the cognition domain and rescoring the swallow domain. The proposed post hoc primary endpoint is change in R4DNPCCSS score from baseline to last visit while on treatment. For this endpoint, based on the Applicant's analysis of covariance (ANCOVA), the estimated treatment difference is -1.51 (95% CI: -2.95, -0.06; nominal p=0.0413).

Although the results of the Applicant's post hoc analysis of the R4DNPCCSS appear to show a trend toward slower progression in the arimoclomol arm compared to the placebo arm during the 12-month double-blind period of Study NPC-002, the review team's post hoc analyses, as discussed in Section 3.1.3.2, show uncertainty regarding the estimated treatment effect. The review team also has concerns regarding the validity of the primary endpoint, which are discussed in Section 3.1.3.3. Therefore, there is uncertainty regarding the strength of the evidence from Study NPC-002 to demonstrate that arimoclomol is effective in patients with NPC.

In this study, most subjects (78%) were receiving concomitant miglustat therapy. Because only a very small subgroup of subjects was on arimoclomol alone, we cannot draw definitive conclusions on the response in that group.

The proposed confirmatory evidence was comprised of nonclinical and clinical pharmacology data, as well as additional clinical data from the open label-extension of study NPC-002, the observational study NPC-001, natural history data from the ongoing NIH natural history study of NPC, and patients with NPC treated with arimoclomol under expanded access protocols. Such sources of evidence may be acceptable sources of confirmatory evidence, as outlined in the aforementioned FDA draft guidance *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). These lines of evidence intended to serve as confirmatory evidence are discussed in detail in Section 3.1.3.4. The Agency seeks the Committee's perspective on the strengths and limitations of support the confirmatory evidence provides towards a conclusion that the drug is effective.

Given the uncertainty regarding the estimated treatment effect in Study NPC-002, the challenges in interpreting the primary endpoint, and the nature of the confirmatory evidence, FDA is seeking your input regarding the effectiveness of arimoclomol in NPC. Specifically, we seek your assessment of: 1) the strengths and limitations of evidence based upon the clinical trial; 2) the strengths and limitations of evidence emerging from the package of confirmatory evidence; and 3) whether the evidence from these two sources together supports a conclusion that arimoclomol is effective in the treatment of NPC.

3.1.3 Efficacy in Detail

3.1.3.1 Niemann-Pick Disease Type C Clinical Severity Scale Background and Limitations

The Niemann-Pick disease type C Clinical Severity Scale (NPCCSS) was used to assess the primary efficacy outcome in Study NPC-002. The NPCCSS has been used broadly in NPC clinical care globally for at least 15 years and has played an important role in furthering the understanding of the complex nature of the progressive symptoms of NPC. While other NPC severity scales have been included in clinical research, more recently, abbreviated versions of the NPCCSS that focus on the symptoms that are most meaningful to patients have been used in several non-interventional and interventional clinical trials.

The NPCCSS is a clinician-reported outcome measure, which was originally based on a 4-domain (ambulation, fine motor, swallow, speech) NPC-specific disability scale (Iturriaga et al. 2006) that was modified and expanded into a 17-domain severity scale to characterize and quantify NPC disease severity and progression for retrospective characterization and prospective patient monitoring (Yanjanin et al. 2010). The NPCCSS was intended to characterize clinical signs and symptoms of NPC across 9 major domains (ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, swallow) rated by clinicians on an ordinal response scale with ratings from 0 to 5, where higher ratings indicate greater clinical severity. Eight minor domains (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory problems) are rated on a three-level response scale from zero to two, with higher ratings indicating greater clinical severity. The 17-domain version of the NPCCSS was used in Study NPC-002.

In response to FDA advice to assess the most relevant signs of NPC across the age spectrum in the target patient population, the Applicant conducted qualitative research with patients, caregivers, and clinical experts to identify the most clinically relevant domains of NPCCSS. The five domains determined to be the most relevant to patients, caregivers, and clinical experts were ambulation, fine motor skills, swallow, cognition, and speech.

The 5-domain Niemann-Pick disease type C Clinical Severity Scale (5DNPCCSS) comprises these five domains. The 5DNPCCSS total score is computed as the sum of the domain scores (0 to 5) and ranges from 0 to 25, where a higher 5DNPCCSS score indicates a higher symptom burden or level of disease

progression. Notably, the response categories corresponding to the 0 to 5 ratings for each domain are not linear. For example, there are no response categories corresponding to a rating value of 3 for ambulation and fine motor and there is no response category corresponding to a rating value of 2 for the cognition domain. A total score is only computed in the presence of complete domain response data. The 5DNPCCSS was administered as part of the full 17-domain NPCCSS in Study NPC-002 and 5DNPCCSS scores were computed based on responses to select domains on the full NPCCSS. The ambulation, speech, swallowing, fine motor, and cognition domains of the NPCCSS appear in Figure 2. The full NPCCSS as administered in NPC-002 appears in Section 5.2.

Figure 2. The Ambulation, Speech, Swallowing, Fine Motor, and Cognition Domains of the NPCCSS as Administered in Study NPC-002

Ambulation	Score =
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18 months	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5
Speech	**Score =**
Normal speech	0
Mild dysarthria (easily understood)	1
Severe dysarthria (difficult to understand)	2
Non-verbal/functional communication skills for needs	3
Minimal communication	5
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
Fine Motor Skills	**Score =**
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/Dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for self-care activities)	5

Cognition	Score =
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum or modified work setting	3
Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function	4
Minimal cognitive function	5

Source: Applicant's COA Dossier Version 4.0, Date 26 May 2020. Appendix C
*Score is additive across cough, liquids, and solids. See Table 8 for details.
Abbreviations: NPC, Niemann-Pick disease type C; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale

Uncertainties with the 5DNPCCSS and its implementation in NPC-002 were raised by the Agency during the IND phase, specifically whether:

- All five domains were well-defined;
- All five domains were sensitive to change over the duration of treatment in NPC-002;
- All five domain scores measure the concepts they intend to (i.e., domain scores have the psychometric property of validity);
- All five domain scores measure the concepts they intend to measure consistently across time and raters (i.e., domain scores have the psychometric property of reliability);
- The 5DNPCCSS could be administered in a standardized manner throughout NPC-002.

Additionally, the Agency noted that the cognition domain ratings relied on the patient environment (e.g., access to services) and may not be adequately evaluated or sensitive to change within the 12-month trial by a severity scale. Regarding the swallow domain, during the review of the initial NDA submission, the Agency had concerns about whether the response options overlapped, were ordered to reflect increasing disease severity, and allowed for comprehensive assessment of swallowing, including silent aspiration.

Given the limitations raised in the review of the original submission, the Applicant proposed to remove the NPCCSS cognition domain score from the 5DNPCCSS total score to create the 4DNPCCSS total score. In the Type A End-of-Review meeting held on October 13, 2021, the Agency agreed with the proposal to remove the NPCCSS cognition domain from the NPCCSS endpoint as the domain was not considered fit-for-purpose. At the August 10, 2023, Type B meeting, the Applicant proposed revised scoring for the swallow domain, resulting in the rescored 4-domain NPCCSS (R4DNPCCSS) score used in the current analyses. The remaining uncertainties with the R4DNPCCSS will be discussed in Section 3.1.3.3.

3.1.3.2 Efficacy Results in Study NPC-002

Section 3.1.3.2.1 presents the efficacy results for the prespecified primary 5DNPCCSS endpoint in the original submission, Section 3.1.3.2.3 presents the efficacy results for the post hoc R4DNPCCSS endpoint in the resubmission, and Section 3.1.3.2.4 provides a summary of the efficacy results.

3.1.3.2.1 Results for Primary 5DNPCCSS Endpoint in Study NPC-002

The prespecified primary endpoint in Study NPC-002 is change from baseline to month 12 in 5DNPCCSS (referred to as the 5DNPCCSS endpoint in this document). The Applicant's prespecified primary analysis method for the primary endpoint in the statistical analysis plan (SAP) is a MMRM. The MMRM includes

treatment, visit (months 3, 6, 9, and 12), treatment-by-visit interaction, baseline miglustat use (yes/no), and baseline 5DNPCCSS score.

As presented in Table 3, based on the Applicant's prespecified MMRM, the estimated treatment difference is -1.4 (95% CI: -2.76, -0.03; p-value=0.0456) and meets the statistical significance level (two-sided p-value<0.05). The estimated treatment difference of -1.4 appears to be driven by three domains: swallow, speech, and fine motor skills. For these three domains, the observed mean change from baseline to 12 months was lower for the arimoclomol arm compared to the placebo arm: swallow (0.1 versus 0.6), speech (-0.1 versus 0.3), and fine motor skills (0.3 versus 0.6). For additional numerical details of each domain in 5DNPCCSS, see Table 25.

However, as discussed in the next section, FDA notes limitations of the prespecified MMRM analysis in terms of handling of "early escape" and death. The FDA's post hoc analyses with different handling of death and early escape provide smaller estimates of treatment difference with nominal values of p>0.05 (Table 3). A detailed discussion of the FDA's post hoc analyses is provided in the next section.

Table 3. Efficacy Results for Prespecified Primary 5DNPCCSS Endpoint

Variable	Arimoclomol (N=34)	Placebo (N=16)	Difference (95% CI)	p-value
Baseline 5DNPCCSS, Mean (SD)	12.1 (6.9)	9.4 (6.4)		
Estimated Change, Mean (SE)				
Applicant's prespecified MMRM[1]	0.72 (0.40)	2.12 (0.55)	-1.40 (-2.76, -0.03)	0.0456
Agency's post hoc analyses				
MMRM1[2]	0.93 (0.44)	2.14 (0.61)	-1.20 (-2.72, 0.32)	0.1186
MMRM2[3]	1.22 (0.45)	2.18 (0.64)	-0.97 (-2.55, 0.62)	0.2264
ANCOVA[4] (while-on-treatment estimand)	0.99 (0.41)	2.16 (0.60)	-1.17 (-2.65, 0.31)	0.1184

Source: FDA's analyses.
[1] Applicant's MMRM excludes data collected after early escape and treats data after death as missing.
[2] Agency's MMRM1 excludes data collected after early escape and uses the worst score of 25 as outcomes for visits after death.
[3] Agency's MMRM2 includes data collected after early escape and uses the worst score of 25 as outcomes for visits after death.
The three MMRM analyses used an unstructured variance-covariance matrix for repeated measures.
[4] Agency's ANCOVA includes baseline miglustat use (yes/no) and baseline 5DNPCCSS score. For this analysis, the endpoint is defined as change from baseline in 5DNPCCSS from baseline to 12 month or to last visit prior to study treatment (including open-label use after early escape) discontinuation or death.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; 5DNPCCSS, five-domain Niemann-Pick disease type C Clinical Severity Scale; MMRM, mixed model repeated measure; SD, standard deviation; SE, standard error

3.1.3.2.2 Handling of Death and Early Escape in the Original Submission

As presented in Table 4, among the randomized patients, 17.6% in the arimoclomol arm and 6.2% in the placebo arm discontinued the study prior to 12 months. In the arimoclomol arm, one patient died, and two patients took an "early escape" route during the DB phase.

Per the study protocol, during the DB phase, patients on either arm experiencing severe disease progression were allowed to take an early escape route (see Appendix Section 5.3.1 for the clinical criteria for early escape) where they were treated with open-label arimoclomol for the remaining part of the 12-month DB phase. In the Applicant's prespecified primary efficacy analysis, patients who took the early escape route were censored at the point where they started open-label arimoclomol and any data collected after this time were not included in the analysis.

The patient who died had two 5DNPCCSS scores falling into the SAP-defined window (±4 weeks) for the 6-month visit: score of 18 at Day 162 (scheduled month 6 visit) and score of 25 at Day 193 (unscheduled

visit). The SAP did not specify how to handle 5DNPCCSS scores at unscheduled visits and the Applicant's prespecified MMRM analysis did not use the score of 25 (the worst possible score) at Day 193.

Table 4. Patient Disposition in Blinded Phase of Study NPC-002

Description	Arimoclomol N (%)	Placebo N (%)	Total n (%)
Patients randomized	34 (100)	16 (100)	50 (100)
Completed blinded phase			
Yes	27 (79.4)	15 (93.8)	42 (84.0)
No	7 (20.6)	1 (6.2)	8 (16.0)
Early escape[1]	2 (5.9)	0 (0.0)	2 (4.0)
Reason for study discontinuation			
Withdrawal by parent/guardian	2 (5.9)	0 (0.0)	2 (4.0)
Death	1 (2.9)	0 (0.0)	1 (2.0)
Safety reasons	3 (8.8)	0 (0.0)	3 (6.0)
IMP stop criteria met[2]	0 (0.0)	1 (6.2)	1 (2.0)

Source: Tables 2-8 of the Applicant's Summary of Clinical Efficacy in the original NDA.
[1] After taking the early escape route, one patient discontinued the study prior to 12 months.
[2] Due to worsening of epilepsy, IMP administration was not possible.
Abbreviations: IMP, investigational medicinal product.

For patients who took early escape or died prior to month 12, the Applicant's prespecified MMRM analysis envisions hypothetical 5DNPCCSS scores at the visits after early escape or death as if they had adhered to their blinded treatments through month 12 and treats such hypothetical 5DNPCCSS scores as missing. From FDA's perspective, it is not reasonable to assume hypothetical 5DNPCCSS scores at the visits after death. In addition, FDA noted that the data excluded from the prespecified analysis indicated worsening in the 5DNPCCSS score for the two patients who took early escape and for the patient who died in the arimoclomol arm.

To investigate the impact of handling of early escape and death, FDA considers the following two post hoc MMRM analyses:

1. MMRM which uses the score of 25 as month 9 and month 12 outcomes for the patient who died and does exclude the data collected after early escape as the prespecified MMRM does (referred to in Table 3 as the "FDA's MMRM1").
2. MMRM which uses the score of 25 as month 9 and month 12 outcomes for the patient who died and does not exclude any data collected after early escape (referred to in Table 3 as the "FDA's MMRM2").

As another post hoc analysis, FDA also considers an ANCOVA for change in 5DNPCCSS score from baseline to month 12 or to last visit prior to study treatment (including open-label use after early escape) discontinuation or death. The ANCOVA model includes baseline miglustat use (yes/no) and baseline 5DNPCCSS score. The results of the ANCOVA are similar to those from the Agency's MMRM1. As alluded in the FDA's Complete Response letter for the original NDA, this ANCOVA estimated a while-on-treatment estimand.

3.1.3.2.3 Results for Post Hoc R4DNPCCSS Endpoint in Study NPC-002

3.1.3.2.3.1 Methodology: Applicant's Proposal and FDA Post Hoc Approaches for Resubmission

In the NDA resubmission, the Applicant proposed to use the rescored 4-domain NPCCSS (R4DNPCCSS) score as the primary efficacy outcome. The R4DNPCCSS score is obtained by removing the cognition

domain and rescoring the swallow domain in the 5DNPCCSS score (Section 5.3.2). The proposed post hoc primary efficacy endpoint for the resubmission is "change in R4DNPCCSS score from baseline to last visit while on treatment" (referred to as the R4DNPCCSS endpoint in this document). For a subject who completes the DB phase of the study, the outcome of this endpoint is change in R4DNPCCSS from baseline to month 12. For a subject who prematurely discontinued the study or died prior to month 12, the outcome of this endpoint is change in R4DNPCCSS from baseline to last visit. This endpoint incorporates the data after early escape for two subjects and the last measurement for the subject who died.

Regarding the analytical method for the R4DNPCCSS endpoint, the Applicant proposes to use an ANCOVA model including baseline miglustat use (yes/no) and baseline R4DNPCCSS score, which is different from the MMMR analysis prespecified for the protocol-defined 5DNPCCSS endpoint. This ANCOVA analysis for the R4DNPCCSS endpoint (change in R4DNPCCSS score from baseline to last visit while on treatment) is referred to as "while-on-treatment" strategy in this document.

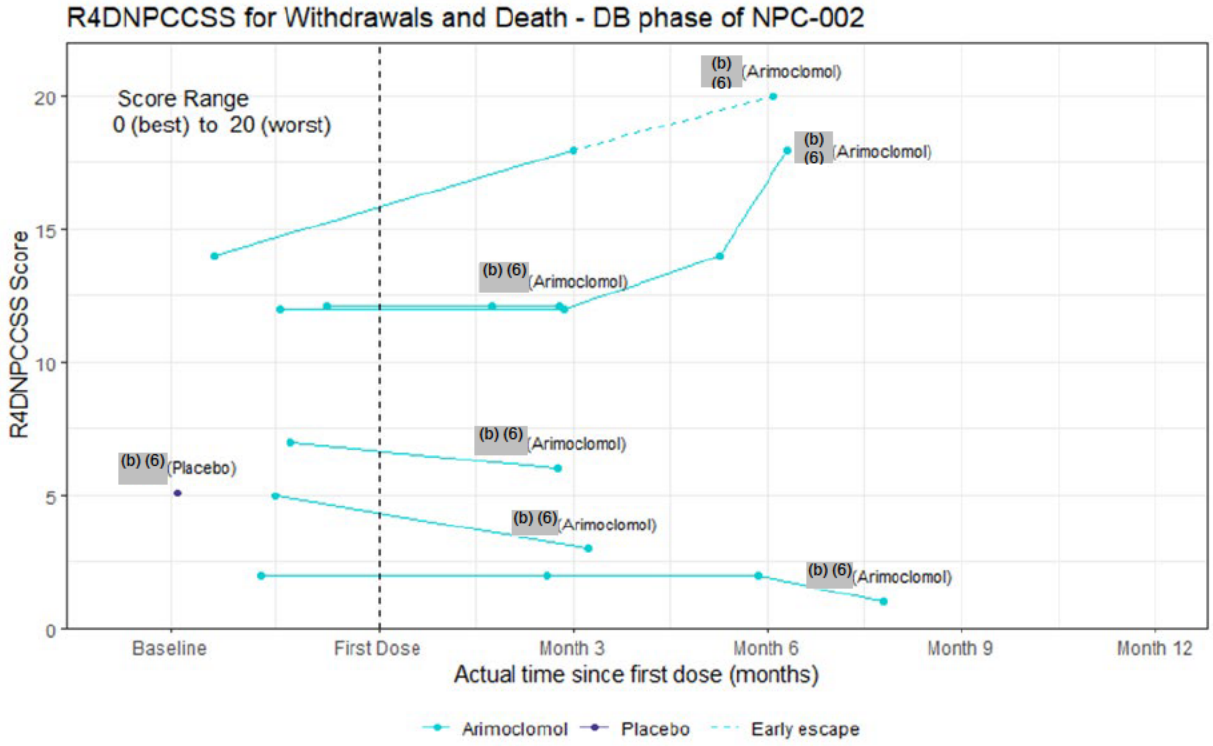
For a comprehensive evaluation of efficacy data in the resubmission, FDA also considers a post hoc endpoint of change in R4DNPCCSS score from baseline to month 12. For a subject who prematurely discontinued the study prior to month 12, outcome of this endpoint is considered as missing. This endpoint is analyzed using the MMRM analysis prespecified for the primary 5DNPCCSS endpoint in the original submission. In addition, the FDA's two post hoc MMRM analyses for the primary 5DNPCCSS endpoint (MMRM1 and MMRM2 in Table 3) are repeated for this endpoint. The three MMRM analyses are referred to as "hypothetical" strategies in this document. Of note, the MMRM analyses do not explicitly impute missing values for subjects who prematurely discontinued prior to month 12.

As additional post hoc analyses for the endpoint of change in R4DNPCCSS score from baseline to month 12, FDA also considers ANCOVA analyses with explicit imputation of missing values, which are referred to as "treatment-policy" strategies in this document. See the next subsection for details of the FDA's approaches for imputing missing values in the treatment-policy strategies.

3.1.3.2.3.2 FDA Approaches to Impute Missing Values in Treatment-Policy Strategies

Figure 3 depicts the R4DNPCCSS over time for subjects who prematurely discontinued the study or died prior to 12 months. Patient (b) (6) died due to cardiorespiratory arrest. In the FDA's treatment-policy strategies, outcome of the endpoint for this subject is defined as the worst change from baseline prior to death. The rest of the 6 patients in the figure prematurely discontinued the study prior to 12 months: patients (b) (6) due to adverse events, patient (b) (6) due to consent withdrawal, and (b) (6) due to consent withdrawal after early escape. In the FDA's treatment-policy strategies, missing data at month 12 for these 6 patients are imputed as described below.

Figure 3. R4NPCCSS Score Over Time for Withdrawals and Death in Study NPC-002



Source: FDA's figure.
Abbreviations: DB, double-blind; R4DNPCCSS, Re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale

The FDA considers three imputation methods which assume that a patient who reached the worst possible score of 20 remains the same after treatment discontinuation. This assumption appears reasonable because no spontaneous improvement is expected after treatment discontinuation. For the other subjects who did not complete the study, their missing data are imputed as follows:

1. Method 1 uses the worst observed change within each patient during the DB phase.
2. Method 2 uses the maximum value between the worst observed change within each patient during the DB phase and the median change at 12 months in the placebo group.
3. Method 3 is a multiple imputation method. The multiple imputation 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.

Method 1 assumes that a patient's disease severity at 12 months is the same as the worst observed disease severity prior to treatment discontinuation; Method 2 additionally assumes that the degree of worsening from baseline to 12 months for a patient with treatment discontinuation is at least the median level of worsening observed in the placebo group; Method 3 assumes that other patients behave like placebo-treated patients after treatment discontinuation.

3.1.3.2.3.3 Imputed Values for Missing Data in FDA's Treatment-Policy Strategies

Table 5 presents the imputed change from baseline to month 12. For the five patients at the bottom of the table, multiple imputation was implemented as described above. For these 5 patients, the table

presents mean (standard deviation) among 100 imputed values within each subject. For patient (b) (6) who reached the worst score possible (20), there is no difference in the imputed values across the methods. Method 2 and Method 3 are likely to lead to more conservative results than Method 1 as the imputed values in Method 2 and Method 3 are larger than those in Method 1 and the majority of the six patients is in the arimoclomol arm.

Table 5. Imputed Change from Baseline to Month 12 in R4DNPCCSS for Treatment-Policy Estimand in Study NPC-002

Patient ID	Arm	Change From Baseline To Last Visit	Imputed Change From Baseline to Month 12		
			Method 1	Method 2	Method 3
(b) (6)	Arimoclomol	6 (from 14 to 20)	6	6	6
	Arimoclomol	0 (from 12 to 12)	0	1	1.96 (3.2)
	Arimoclomol	-1 (from 7 to 6)	0	1	1.44 (2.5)
	Arimoclomol	-2 (from 5 to 3)	0	1	1.98 (3.0)
	Arimoclomol	-1 (from 2 to 1)	0	1	1.68 (2.9)
	Placebo	0 (from 5 to 5)	0	1	2.11 (3.2)

Source: FDA's table.
Abbreviations: ID, identification; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; R4DNPCCSS, re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale

3.1.3.2.3.4 Results of Post Hoc Analyses for R4DNPCCSS

Table 6 presents the results of the post hoc analyses for the R4DNPCCSS endpoint. The analysis using the while-on-treatment strategy (proposed as primary by the Applicant in the resubmission), the analysis using the MMRM prespecified for the 5DNPCCSS endpoint, and the analysis using the FDA's MMRM1 provide nominal two-sided p-values smaller than 0.05 while the other analyses do not. The estimated treatment difference is -1.51 (95% CI: -2.95, -0.06) in the while-on-treatment strategy. The estimated treatment difference in the hypothetical strategy ranges from -1.28 to -1.70, depending on handling of the data after early escape and the last measurement for the subject who died. The estimated treatment difference in the treatment-policy strategy ranges from -1.17 to -1.29, depending on the methods for imputing the missing data.

Table 6. Summary of Rescored 4-Domain NPCCSS (R4DNPCCSS) Score in Study NPC-002

Parameter	Arimoclomol	Placebo	Difference (95% CI)	p-value
Score at baseline	N=34	N=16		
Mean (SD)	9.2 (5.8)	6.7 (5.2)		
Median (min, max)	8.5 (1.0, 20.0)	5.0 (0.0, 19.0)		
Score at 12 months	N=28	N=15		
Mean (SD)	9.9 (6.6)	8.7 (6.5)		
Median (min, max)	9.5 (0.0, 20.0)	7.0 (0.0, 20.0)		
Change from baseline at 12 months	N=28	N=15		
Mean (SD)	0.6 (2.2)	1.9 (3.1)		
Median (min, max)	0.0 (-2.0, 8.0)	1.0 (0.0, 12.0)		

Parameter	Arimoclomol	Placebo	Difference (95% CI)	p-value
Estimated mean change (SE)				
Hypothetical strategy				
Applicant's Prespecified MMRM[1]	0.33 (0.40)	2.02 (0.54)	-1.70 (-3.05, -0.34)	0.0155
Agency's MMRM1[2]	0.44 (0.41)	2.04 (0.56)	-1.60 (-3.00, -0.19)	0.0265
Agency's MMRM2[3]	0.79 (0.44)	2.06 (0.63)	-1.28 (-2.83, 0.28)	0.1056
Applicant's while-on-treatment strategy[4]	0.62 (0.39)	2.12 (0.59)	-1.51 (-2.95, -0.06)	0.0413
Agency's treatment-policy strategy[5]				
Method 1 (worst change)	0.73 (0.39)	2.01 (0.57)	-1.29 (-2.68, 0.11)	0.0695
Method 2 (placebo median)	0.85 (0.39)	2.06 (0.57)	-1.21 (-2.61, 0.20)	0.0899
Method 3 (multiple imputation)	0.95 (0.46)	2.12 (0.66)	-1.17 (-2.76, 0.43)	0.1523

Source: FDA's analyses.

[1] Estimated mean change (SE) from baseline to 12 months by the Applicant's MMRM prespecified for the 5DNPCCSS endpoint. The Applicant's MMRM excludes data collected after early escape and treats data after death as missing.

[2] Agency's MMRM1 excludes data collected after early escape and uses the worst score of 18 as outcomes for visits after death.

[3] Agency's MMRM2 includes data collected after early escape and uses the worst score of 18 as outcomes for visits after death.

The three MMRM analyses used an unstructured variance-covariance matrix for repeated measures.

[4] Estimated mean change (SE) from baseline at 12 months or last visit prior to study discontinuation by the Applicant's ANCOVA model adjusted for baseline R4DNPCCSS score and baseline miglustat use (yes/no).

[5] Estimated mean change (SE) from baseline at 12 months by the Agency's ANOCVA model adjusted for baseline R4DNPCCSS score and baseline miglustat use (yes/no); Method 1 used the worst change within each patient; Method 2 used the maximum value between the worst change within each patient and the median change (1.0) in the placebo group; Method 3 used multiple imputation based on the observed distribution of change from baseline to 12 months in the placebo group.

Abbreviations: 5DNPCCSS, five-domain Niemann-Pick disease type C Clinical Severity Scale; ANCOVA, analysis of covariance; CI, confidence interval; MMRM, mixed model repeated measure; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; R4DNPCCSS, re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale SD, standard deviation; SE, standard error

The efficacy results for R4DNPCCSS are contributed by three domains: swallow, speech, and fine motor skills (Table 25). For example, using the treatment-policy strategy, the estimated treatment difference was -0.45 (95% CI: -1.15, 0.25; p-value=0.2004) for the rescored swallow domain, -0.26 (95% CI: -0.83, 0.30; p-value=0.3507) for the speech domain, and -0.18 (95% CI: -0.74, 0.38; p-value=0.5272) for fine motor skills. Note: for the swallow domain in the original score, the estimated treatment difference was -0.28 (95% CI: -0.97, 0.40; p-value=0.4115).

Table 7 presents the analysis results of the 4DNPCCSS endpoint which is obtained by just removing the cognition domain from the 5DNPCCSS endpoint (i.e., without rescoring of swallow domain). The estimated treatment difference is -1.27 (95% CI: -2.63, 0.08) in the while-on-treatment strategy. The estimated treatment difference in the hypothetical strategy ranges from -1.27 to -1.54, depending on handling the data after early escape and the last measurement for the subject who died. The estimated treatment difference in the treatment-policy strategy ranges from -0.96 to -1.12, depending on the methods for imputing the missing data.

Table 7. Summary of 4-Domain NPCCSS (NPCCSS) Score in Study NPC-002

Parameter	Arimoclomol	Placebo	Difference (95% CI)	p-value
Score at baseline	N=34	N=16		
Mean (SD)	9.3 (5.9)	6.9 (5.2)		
Median (min, max)	9.0 (1.0, 20.0)	5.5 (0.0, 19.0)		
Score at 12 months	N=28	N=15		
Mean (SD)	10.1 (6.7)	8.9 (6.4)		
Median (min, max)	10.0 (0.0, 20.0)	7.0 (0.0, 20.0)		
Change from baseline at 12 months	N=28	N=15		
Mean (SD)	0.6 (2.2)	1.9 (2.8)		
Median (min, max)	0.0 (-2.0, 8.0)	1.0 (0.0, 11.0)		
Estimated change, mean (SE)				
Hypothetical strategy				
Applicant's Prespecified MMRM[1]	0.43 (0.37)	1.97 (0.51)	-1.54 (-2.82, -0.26)	0.0193
Agency's MMRM1[2]	0.57 (0.40)	1.99 (0.55)	-1.42 (-2.79, -0.05)	0.0430
Agency's MMRM2[3]	0.84 (0.42)	2.03 (0.59)	-1.18 (-2.65, 0.28)	0.1104
Applicant's while-on-treatment strategy[4]	0.71 (0.38)	1.98 (0.55)	-1.27 (-2.63, 0.08)	0.0650
Agency's treatment-policy strategy[5]				
Method 1 (worst change)	0.84 (0.37)	1.96 (0.55)	-1.12 (-2.46, 0.22)	0.0989
Method 2 (placebo median)	0.94 (0.37)	2.01 (0.55)	-1.07 (-2.42, 0.28)	0.1176
Method 3 (multiple imputation)	1.07 (0.46)	2.03 (0.63)	-0.96 (-2.51, 0.60)	0.2275

Source: FDA's analyses.

[1] Estimated mean change (SE) from baseline to 12 months by the Applicant's MMRM prespecified for the 5DNPCCSS endpoint. The Applicant's MMRM excludes data collected after early escape and treats data after death as missing.

[2] Agency's MMRM1 excludes data collected after early escape and uses the worst score of 18 as outcomes for visits after death.

[3] Agency's MMRM2 includes data collected after early escape and uses the worst score of 18 as outcomes for visits after death.

The three MMRM analyses used an unstructured variance-covariance matrix for repeated measures.

[4] Estimated mean change (SE) from baseline at 12 months or last visit prior to study discontinuation by the Applicant's ANCOVA model adjusted for baseline R4DNPCCSS score and baseline miglustat use (yes/no).

[5] Estimated mean change (SE) from baseline at 12 months by the Agency's ANCOVA model adjusted for baseline R4DNPCCSS score and baseline miglustat use (yes/no); Method 1 used the worst change within each patient; Method 2 used the maximum value between the worst change within each patient and the median change (1.0) in the placebo group; Method 3 used multiple imputation based on the observed distribution of change from baseline to 12 months in the placebo group.

Abbreviations: 5DNPCCSS, five-domain Niemann-Pick disease type C Clinical Severity Scale; ANCOVA, analysis of covariance; CI, confidence interval; MMRM, mixed model repeated measure; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; R4DNPCCSS, re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale; SD, standard deviation; SE, standard error

3.1.3.2.3.5 Subgroup Analysis Results for Post Hoc R4DNPCCSS Endpoint In Study NPC-002

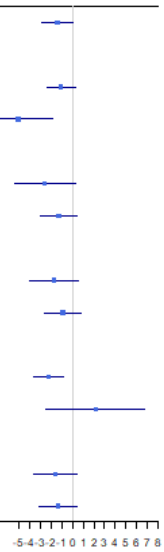
Figure 4 presents the subgroup analysis results by baseline age, age at first neurological symptoms, sex, miglustat use, and baseline R4DNPCCSS score. Except for the subgroup of subjects who did not take miglustat, the estimated treatment difference in all subgroups numerically favor the arimoclomol arm. For the subgroup of subjects who did not take miglustat, the estimated treatment difference numerically favors the placebo arm. However, it is difficult to interpret this subgroup analysis given the small sample size (three in the placebo arm and eight in the arimoclomol arm) and the following baseline imbalances between the treatment arms that indicated worse disease prognosis in the arimoclomol arm:

1. The median baseline R4DNPCCSS score is 5 in the placebo arm and 11 in the arimoclomol arm (Table 28).
2. The median age at first neurological symptoms is 10 years in the placebo arm and 3.5 years in the arimoclomol arm (Table 27).

Table 28 presents detailed efficacy results by miglustat use. Figure 37 and Figure 38 show the R4DNPCCSS score over time by miglustat use. Table 27 presents detailed summary statistics of key baseline characteristics by miglustat use. Among the subjects who did not use miglustat at baseline, those who had both early onset of neurological symptoms and a high severity score at baseline experienced a significant disease progression at 12 months (Table 29).

Figure 4. Analyses of R4DNPCCSS Score in Subgroups by Baseline Age, Age at First Neurological Symptoms, Sex, Miglustat Use, and Baseline Score

	Arimoclomol	Placebo	Difference
Subgroup	N / Mean	N / Mean	(95% CI)
Overall	34 / 0.60	16 / 2.04	-1.4 (-2.8, -0.0)
Age at baseline			
< 12 years	16 / 1.04	11 / 2.13	-1.1 (-2.4, 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 / 0.68	13 / 2.00	-1.3 (-3.0, 0.4)
Sex			
Female	17 / 0.35	9 / 2.11	-1.8 (-4.1, 0.6)
Male	17 / 0.90	7 / 1.82	-0.9 (-2.7, 0.8)
On miglustat			
Yes	26 / -0.39	13 / 1.85	-2.2 (-3.7, -0.8)
No	8 / 4.13	3 / 1.98	2.2 (-2.5, 6.8)
Baseline score			
<= 8	17 / 0.19	12 / 1.81	-1.6 (-3.7, 0.4)
> 8	17 / 1.07	4 / 2.46	-1.4 (-3.2, 0.4)



Source: FDA's analysis. For each subgroup, the estimated mean change from baseline to 12 months or last visit prior to study discontinuation and its difference (95% CI) were obtained from ANCOVA models. The ANCOVA models were adjusted for baseline R4DNPCCSS score and miglustat use for the subgroups by age, age at first neurological symptoms, sex, and baseline R4DNPCCSS. The ANCOVA models for subgroups by miglustat use was adjusted for baseline R4DNPCCSS score. Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; R4DNPCCSS, re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale

3.1.3.2.4 Overall Assessment of Efficacy Data From Double-Blind Phase of Study NPC-002

The prespecified primary analysis for the primary 5DNPCCSS endpoint in the original submission meets the statistical significance level (two-sided p-value<0.05). However, as discussed above, this analysis has limitations due to exclusion of the data after patients "escape" (two patients "escape" in the arimoclomol arm) and the data at the last unscheduled visit for the patient who died in the arimoclomol arm, and it was notable that the excluded data indicated disease worsening. FDA's post hoc analyses including these data yielded smaller estimated treatment differences.

For the post hoc R4DNPCCSS endpoint in the resubmission, the FDA's post hoc analyses numerically favored the arimoclomol arm. Some of the analyses provide nominal p-values smaller than 0.05 while the others do not. While there is uncertainty regarding the estimated treatment effect for both the 5DNPCCSS endpoint and the R4DNPCCSS endpoint, the point estimates in the multiple analyses appear to show slower progression in the arimoclomol arm compared to that in the placebo arm during the 12-month double-blind period of Study NPC-002.

Note that there are concerns regarding the validity of these endpoints as discussed in Section 3.1.3.3, which may impact the clinical interpretation of the estimated treatment effects.

We ask the Advisory Committee to consider whether the presented results support a treatment effect of arimoclomol.

3.1.3.3 Assessment of the Validity of the Rescored 4-domain Niemann-Pick Disease Type C Clinical Severity Scale (R4DNPCCSS)

Key uncertainties remain with the R4DNPCCSS including (1) standardized administration, (2) response option scoring, and (3) comprehensive assessment of NPC symptoms (speech, swallow, ambulation, fine motor).

Standardized Administration

Standardized administration of a clinical outcome assessment (COA) helps ensure that data are valid and reliable. Typically, standardized data collection specifies who (e.g., parent/caregiver, clinician) is meant to provide what information about the patient's level of impairment over what duration of time (i.e., the recall/assessment period) and in what context (e.g., the patient's daily life [via parent/caregiver report], real-time clinical evaluation conducted through direct observation of the patient [via clinician report]). Standardized administration and well-defined scoring procedures many times include:

- Training materials used to help caregivers evaluate the patient's level of impairment with respect to each domain to which the caregiver report contributes, including those domains to which the caregiver report contributes to the clinician's rating via direct observation in everyday life;
- A daily diary or other measurement approaches for caregivers to systematically record their observations;
- Standardized clinical evaluation procedures conducted to inform the scoring of each domain to which clinician report contributes; and
- Specification of how, for each domain, a response option is to be selected if a patient's level of impairment in that functional area varied over the duration of the assessment period.

Beyond this specific drug development program, in settings where the assessment used in the clinical trial is the one used in clinical practice, there has been discussion over how much standardization and training related to the assessment is needed within a clinical trial. In NPC-002, the Applicant provided clinicians with an NPCCSS scoring manual as well as a training presentation. No training materials were provided to caregivers. The Applicant also did not provide caregivers daily diaries to collect observations, although it is important to note that each caregiver may have had their own system for summarizing information to aid their regular communication with their clinical care team. During qualitative interviews of clinicians who were part of and not part of NPC-002, clinicians indicated that standard practice when scoring the NPCCSS involves the clinician observing the patients as well as asking the patient and/or caregiver to provide a characterization of recent everyday life level of function or impairment. Additionally, these clinicians raised potential differences across individuals in steps that would be taken to determine a rating (e.g., ordering a functional swallow assessment); however, the importance of those differences may be diminished when looking at change from baseline if the same caregiver and same clinician are working together longitudinally. The Applicant stated that individual participants were rated by the same clinician through the trial "if at all feasible"; however, it is unclear who performed the rating and which caregiver(s) provided information at each study visit. The lack of evidence of standardization procedures in Study NPC-002 reduces our confidence in the reliability of the

responses collected. Given the specific trial setting and assessment, FDA is interested in the panel's thoughts on the impact (including potential lack of impact) of the processes used to assess the endpoint in NPC-002.

Response Options and Scoring

In each of the domains, there are adjacent responses that may not be sufficiently distinct such that there may have been overlap in how raters scored particular items in a domain.

Ambulation

Regarding ambulation, two response options refer to the patient's ambulatory functioning at specific chronological ages, measuring whether the patient experienced "ataxic unassisted gait or not walking by 18 months" (ambulation domain score =2) or "assisted ambulation or not walking by 24 months" (ambulation domain score =3). A patient's level of ambulation impairment at a static point in time (e.g., at a specific chronological age) cannot change in response to treatment.

Fine Motor

One uncertainty with the fine-motor skills domain is the unclear distinction between two of the rating levels. The severity levels for the fine-motor skills domain are described in terms of feeding abilities, an important functional ability. The difference between "slight dysmetria/dystonia (independent manipulation)" (fine motor domain score =1) and "mild dysmetria/dystonia (requires little to no assistance, able to feed self without difficulty)" (fine motor domain score =2) may be difficult for clinician raters to consistently, reliably differentiate without a clearly operationalized definition of the difference between "slight" and "mild." The lack of clarity between these two levels may lead to mixed ratings by clinicians, where some may assign a score of 1 and others a 2 for the same patient presentation.

Speech

The speech domain assesses multiple complex aspects of communication including dysarthria (e.g., a slowed verbal pace, slurring of verbal speech, word finding problems) and non-verbal communication (e.g., hand signals and/or sign language, keyboard skills, gestures). Given the diverse aspects of communication included, this domain may not be well-defined and sufficiently focused to support clinical trial measurement. It was also unclear how clinician raters differentiate between the levels, including the two most severe levels of the domain, specifically "non-verbal/functional communication skills for needs" and "minimal communication."

Swallow

Uncertainties for the swallow domain were that the response options and corresponding scores appeared to be overlapping and unclearly ordered by disease severity (Table 8). Specifically, scores should be distinct and used only to describe one clinically distinct presentation, yet it appeared that different clinical presentations could receive the same score.

Table 8. 5DNPCCSS Swallow Domain Response Options

5DNPCCSS Swallow Domain	Score
Normal, no dysphagia	0
Cough while eating	1
Cough while eating + intermittent dysphagia with liquids	2
Cough while eating + intermittent dysphagia with solids	2
Cough while eating + intermittent dysphagia with liquids + intermittent dysphagia with solids	3
Cough while eating + dysphagia with liquids	3
Cough while eating + dysphagia with solids	3
Cough while eating + intermittent dysphagia with liquids + dysphagia with solids	4
Cough while eating + intermittent dysphagia with solids + dysphagia with liquids	4
Cough while eating + dysphagia with solids + dysphagia with liquids	5
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5

Source: Reviewer's table based on Table 13 in Applicant's COA Evidence Summary Report
Abbreviation: 5DNPCCSS, five-domain Niemann-Pick disease type C Clinical Severity Scale

Further Assessment of the R4DNPCCSS NPC Swallow Domain

In response to the uncertainties raised by the Agency, the Applicant conducted a qualitative semi-structured interview-based study OR-SRV-NPC-04 (hereafter NPC-04), with clinical experts in NPC (n=4 from NPC-002, n=4 independent of the study) and clinical experts in swallowing disorders (n=4). Nearly all 12 experts understood each severity level as intended (ranging from 9 out of 12 for "intermittent dysphagia with liquids" to 12 out of 12 for "dysphagia with liquids"). Three of the NPC experts indicated that interpretation of scores of 2 or 3 and the interpretation of supplemental tube feeding could vary by clinician. All but one expert perceived that the response options were ordered correctly by increasing severity. One expert indicated dysphagia with liquids was more severe than solids given swallowing across the range of abilities. One speech language pathologist thought that it is problematic that silent aspiration is not scored since it is very common in patients with NPC, and when cough disappears over time secondary to progression or desensitization from the aspiration, the patient may appear as improved when they are in fact worsening. An NPC clinical expert stated essentially the opposite: That silent aspiration is an early part of swallow dysfunction that may occur before patients are scored in the "cough while eating category" (a score of 1). These differences in interpretation of the concept of silent aspiration reflect the need for input from a variety of experts to fully examine the complex aspects of measuring and scoring swallow dysfunction. Silent aspiration was not addressed by the Applicant's updated scoring metric because the NPCCSS does not utilize real-time imaging and is not intended to measure aspiration directly. In Study NPC-002, the risk or occurrence of aspiration (silent or otherwise) can only be inferred either by the clinical signs and symptoms of dysphagia, or by the occurrence of recurrent lung infections. Clinical experts made several recommendations for revisions to the scoring, including creating a linear score system. This information indicates that selecting scores in the midrange may vary by clinician (which is expected when applying a severity scale to a complex aspect of functioning) and that from the perspective of most clinical experts, the scale is appropriately ordered by increasing severity for the observable symptoms of swallowing dysfunction it was intended to measure.

Swallowing dysfunction is common in patients with NPC (50 to 80%) and progresses over time. The mechanisms of swallowing dysfunction in NPC are complex and include bulbar dysfunction, dystonia, reduced laryngeal sensation, and cognitive and behavioral differences (Walterfang et al. 2012). These symptoms can also be exacerbated by gastrointestinal symptoms, such as gastroesophageal reflux. The progressive dysphagia in NPC negatively impacts the maintenance of adequate nutrition, weight gain

and hydration and can lead to aspiration and recurrent respiratory illnesses. Respiratory failure due to infection or aspiration is the most common cause of death in NPC.

The swallow domain of the NPCCSS intends to measure swallowing dysfunction in patients with NPC over time. As an observational scale, only the aspects of swallowing that can be observed, described, or felt can be scored. Thus, the oropharyngeal and other observable aspects of dysphagia and feeding are measured, whereas the non-observable aspects of swallowing (e.g., aspiration without a protective airway reflex, or silent aspiration) are not. Non-observable aspects of swallowing dysfunction may be measured with a videofluoroscopic swallow study (VFSS) (Hong et al. 2021). A clinical trial measurement approach that incorporates both the observable and non-observable aspects of swallowing dysfunction in NPC is consistent with NPC clinical management recommendations (Hong et al. 2021) and would have provided a more comprehensive picture of swallowing function in study subjects over time. However, VFSS requires both patient cooperation and ability to participate for the study to be completed, and not all trial sites may be equipped to perform these studies in this patient population.

In response to these uncertainties raised by the Agency, the Applicant submitted the qualitative study NPC-04. This partly resolved some uncertainties. Specifically, clinical experts confirmed that the domain was relevant across the age spectrum, and that caregiver reports were commonly relied on for in-clinic assessment. While all eight NPC experts interviewed indicated swallowing could be reasonably evaluated without a standardized functional assessment (e.g., using in-office food or drink, VFSS), three of the four NPC experts who were not involved in the NPC-002 study indicated they would order a functional test to score the swallow domain (e.g., as part of their routine NPC patient assessment, evaluate penetration with liquids not yet known to the patient, inform patient management and tube feeding). Together these expert opinions appeared to confirm that the NPCCSS swallow domain could reasonably capture observable features of swallow functioning but may not measure subtle but clinically relevant features of aspiration. As such, while the scale may be appropriately ordered by increasing severity for the observable symptoms of swallow dysfunction, it is not clear whether the scale is ordered by increasing severity when accounting for the non-observable aspects of swallowing dysfunction, which the NPCCSS swallow domain is not intended to measure.

To help inform the Agency's evaluation of NPCCSS swallow domain score validity, the Agency conducted cross-sectional and longitudinal exploratory analyses of comparisons of the NPCCSS swallow domain scores to the American Speech-Language-Hearing Association National Outcomes Measurement System and Penetration-Aspiration Scale from an external natural history study (Solomon et al. 2020). Differences in swallow scores were observed across the two pairs of scales in the 0 to 3 range of the NPCCSS swallow scores (based on the original scoring rule[1]), the region of the response scale in which improvement in swallowing was observed in the treatment arm of Study NPC-002. The observed lack of alignment in swallow scores across the scales may have in part reflected the differences in the objectives and response options between the COAs, because the three measures are not intended to assess the same aspects of swallowing. As such, these analyses did not resolve the uncertainty regarding whether NPCCSS swallow scores are a comprehensive representation of a patient's level of swallowing dysfunction.

[1] 0 = Normal. No dysphagia. Based on clinical history/parental or subject report. 1 = cough while eating. Occasional cough but no consistent difficulty swallowing certain texture. 2 = intermittent dysphagia for liquids or solids. OR Dysphagia for liquids or solids at least daily. 4 = Dysphagia for liquids or solids at least daily. OR Nasogastric tube or gastric tube for supplemental feeding. 5 = Nasogastric tube or gastric tube feeding only.

Additionally, issues with a COA like those listed above may make it more difficult to demonstrate a treatment effect in a double-blinded, randomized, controlled trial. This is likely the case for issues such as the ambulation scoring that asks about early child development, which is insensitive to change, and difficulty differentiating slight versus mild dysmetria response options for the fine motor skills domain. However, the direction of any potential shift is uncertain for the swallow domain.

Ambulation, Fine-Motor Skills, and Speech

In response to FDA's request for performance-based validity evidence for NPCCSS domains inclusive of ambulation, speech, and fine motor, the Applicant submitted an information amendment which included Spearman and polychoric correlation coefficients and heatmaps between the relevant NPCCSS domain scores and the corresponding items on the performance-based scale for assessment and rating of ataxia (SARA), which was administered in Study NPC-002. The SARA comprises eight domains, of which the following five assess NPC-relevant symptomatology: gait, speech disturbance, finger chase, nose-finger test, and fast alternating hand movements. The order of administration of the NPCCSS and SARA was not recorded. The correlations among the scores tend to be strong to very strong across the three time points. Clinician raters may or may not have carried over criteria, impressions, or standards from the SARA when administering the NPCCSS, thereby having the SARA act as a guideline for administering the NPCSS ambulation, fine motor, and speech domains. The possibility that clinician raters may have used the criteria or guidelines of the SARA when administering the NPCSS precludes these correlations from providing independent evidence of concurrent validity of these NPCCSS domains.

Conclusion

Given the considerations discussed above, the Advisory Committee is asked to consider whether data from the NPCCSS scale as implemented in NPC-002 can be interpreted to represent a comprehensive assessment of neurological function in NPC including fine motor, speech, swallow, and gait in the context of the arimoclomol development program.

3.1.3.4 Adequacy of the Additional Clinical, Clinical Pharmacology and Nonclinical Evidence to Support a Drug Effect and Together Serve As Confirmatory Evidence of Effectiveness

The Applicant submitted data from multiple sources to serve as confirmatory evidence of the treatment effect of arimoclomol observed in Study NPC-002. These sources, which included nonclinical, clinical pharmacology and clinical studies, are discussed in the sections that follow.

3.1.3.4.1 Nonclinical Evidence

Introduction

The pathogenesis of NPC results from deficiencies in the *NPC1* or *NPC2* genes. Many pathogenic NPC gene defects have been identified which inhibit protein expression by several different mechanisms (null mutations, missense, frameshifts, etc.). Pathogenic mutations in the *NPC1* gene lead to lysosomal accumulation of LDL-cholesterol, with corresponding neuronal degeneration. The mechanism by which lysosomal dysfunction leads to neurodegeneration has not been clearly defined. There are no widely accepted biomarkers for NPC that are used to monitor disease progression or treatment responses in humans or animals.

The Applicant's nonclinical package submitted in support of their NDA consists of a complete set of toxicology studies, including chronic toxicity and embryofetal toxicity studies in rodents and nonrodents;

carcinogenicity studies in rats and mice; and juvenile, fertility and pre- and postnatal development studies in rats.

In the original NDA submission, FDA stated that the confirmatory evidence package, particularly the nonclinical data submitted in support of the proposed MOA, was weak and contradictory. FDA recommended that the Applicant consider additional nonclinical studies to bolster interpretation of the drug's activity and determine whether there is a PD interaction between arimoclomol and miglustat. To that end, the Applicant augmented the submission with additional data to show activity of arimoclomol in the presence of miglustat. What follows is FDA's assessment of the Applicant's package of pharmacology studies submitted in support of this NDA, both data included in the original NDA submission and the resubmission.

Proposed Mechanism of Action

The Applicant proposes that arimoclomol acts to overcome the accumulation of lysosomal cholesterol that results from NPC1/2 deficiency by inducing the expression of genes in the Coordinated Lysosomal Expression and Regulation (CLEAR) pathway; however, the molecular target of arimoclomol has not been defined. In a screen of potential receptors, enzymes, and transporters that the Applicant conducted to identify potential primary and secondary pharmacology targets, there was no significant binding, other than its activity as a 5HT2B agonist, for which half maximum inhibitory concentration was observed at 8.0µM (>1.2-fold the clinical C_{max} of 6.7µM), Ki =4.0µM (>0.6-fold the clinical C_{max}) and binding to the endothelin receptor, for which half-maximal displacement of the canonical ligand was observed at 28µM (>4-fold the clinical C_{max}, 6.7µM).

The CLEAR network is a large network of genes that is involved in cellular metabolism and homeostasis. The primary mediators of the CLEAR network are the ubiquitously expressed transcription factors, TFEB and Transcription Factor E3 (TFE3). Of the 471 gene targets of TFEB (Palmieri et al. 2011), the Applicant chose to focus on 10 genes that are involved in lysosomal function. The CLEAR pathway affects many cellular functions, including autophagy, lysosomal protein expression, biogenesis, acidification, and membrane production. The coordination of these functions is thought to occur through activation of the transcription factors, TFE3 and TFEB, leading to enhanced binding to target gene promoters, and upregulation of mRNA expression from target genes.

The Applicant postulates that activation of the CLEAR network will improve lysosomal function and reduce the quantity of stored unesterified cholesterol in the lysosomes of cells affected by deficiencies in NPC, in part by increasing the expression of chaperone proteins (e.g., HSP1A1) that may affect NPC1 protein folding and thereby increase its expression in late endosomal membranes.

Miglustat is a substrate reduction therapy that inhibits the enzyme glucosylceramide synthase that is involved in the synthesis of glycosphingolipids (GSLs). By blocking this enzyme, miglustat reduces the production of glycosphingolipids, which may be beneficial in treating certain lysosomal storage disorders like Niemann-Pick disease type C and Gaucher disease. Inhibiting the accumulation of GSLs was the rationale for testing miglustat in the treatment of NPC, but miglustat also binds to and affects the activity of other enzymes which may contribute further to its pharmacological effect (Lyseng-Williamson 2014). The effects of miglustat on neurological NPC manifestations has been assessed with a range of approaches, with reported benefits ranging from cellular changes in the brain to visible clinical improvements and improved survival (Pineda et al. 2018). While the effects of miglustat on survival and disease progression have been reported, efficacy in NPC has not been established. Thus, the Applicant

evaluated whether a PD interaction between arimoclomol and miglustat may result in an additive effect compared to arimoclomol or miglustat alone.

The Applicant has provided data from studies in cultured wildtype and patient-derived fibroblasts to characterize gene expression changes resulting from treatment with arimoclomol with or without miglustat, with the intent of defining a potential MOA. They have also evaluated the potential of arimoclomol and/or miglustat to reduce lysosomal lipid accumulation in patient-derived cells. They then evaluated the effects of arimoclomol in two murine models of NPC, a null model that resulted from insertion of a retrotransposon in the coding sequence of the *NPC1* gene ($NPC1^{-/-}$), and a point mutation model ($NPC1^{nmf/nmf}$). In the $NPC1^{-/-}$ model, they also evaluated the effect of miglustat when administered in combination with arimoclomol.

The nonclinical studies that the Applicant provided as sources of data for efficacy are listed in Table 9.

Table 9. Sources of Nonclinical Data

NDA Submission	Nonclinical Study/Study Number	Study Design	Results
Initial	In vitro proof of concept for arimoclomol in NPC patient fibroblasts/ DOC-2004170028 **(Study 28)**	Fibroblast cell lines derived from a panel of 8 NPC patients with mutations on both alleles of NPC1 treated with arimoclomol.	Arimoclomol increased NPC1 expression in fibroblast cell lines from 8 NPC patients with several different disease relevant mutations.
Re-submission	Dose-response expression of HSPA1A, NPC1 and GBA to arimoclomol in GM18453 and GM18420 fibroblasts /DOC-2110140042 **(Study 42)**	Fibroblast cell lines from 2 NPC patients with different mutations, GM18453 (ER mutation) and GM18420 (Lysosomal mutation) evaluated for expression of *NPC1*, *HSPA1A* and *GBA* genes.	Arimoclomol (400µM) increased expression of *HSPA1A*, *NPC1*, and *GBA* genes in fibroblast cell lines from 2 NPC patients.
Re-submission	In vitro effect of arimoclomol on TFE3 localization in human fibroblasts/DOC-2110130040 **(Study 40)**	Fibroblast cell lines from 3 NPC patients: GM18420 (Lysosome mutation), GM18453 (ER mutation), and GM17912 (Lysosome mutation) and wildtype (GM00498) serum starved (cell stress), treated with arimoclomol and evaluated for nuclear localization.	Arimoclomol (400µM) increased nuclear TFE3 localization to a similar degree in all 3 fibroblast cell lines from NPC patients and wildtype fibroblast cell lines.
Re-submission	In vitro effect of arimoclomol on TFE3 and TFEB localization in human fibroblasts and HeLa cells under acute NPC1 inhibition /DOC-2204070049 **(Study 49)**	HeLa or fibroblast cell line (GM00498) pre-treated with NPC1 inhibitor, U18666A and then treated with arimoclomol and evaluated for nuclear translocation.	No clear effect on magnitude of TFE3 nuclear translocation with U18666A; however, appearance of increase in TFE3 nuclear translocation when HeLa cells were co-cultured with arimoclomol and U18666A.

NDA Submission	Nonclinical Study/Study Number	Study Design	Results
Re-submission	Expression of CLEAR genes in GM00498 fibroblasts with arimoclomol treatment/DOC-2110140041 **(Study 41)**	Fibroblast cell line from wildtype (GM00498) treated with arimoclomol in culture for 5 days and assessed for expression of selected CLEAR genes.	Arimoclomol treatment upregulated mRNA expression of several CLEAR genes, including *NPC1*, *NPC2*, *GBA*, *GLA*, *RRAGD*, *MCOLN1*, *SQSTM1*, and *MTIF*.
Re-submission	In vitro effect of arimoclomol on unesterified cholesterol content in human NPC fibroblasts assessed by filipin staining/ DOC-2112170044 **(Study 44)**	Fibroblast cell line from wildtype (GM00498) and NPC patient (GM18453) treated with arimoclomol and assessed with Filipin staining for free cholesterol levels.	There was a very modest, largely non-dose-related reduction in filipin staining at concentrations of 100-200µM.
Initial/ Re-submission	Arimoclomol dosing study in a mouse model of Niemann-Pick Type C disease/CRO-1211210031 **(Study 31)**	Behavioral effects (rearing and gait analysis) and biochemistry endpoints evaluated in $Npc1^{-/-}$ ($Npc1^{nih}$) mice after arimoclomol treatment.	No clear dose-related effects on behavioral parameters (rearing, posture, gait) with arimoclomol treatment up to 300 mg/kg/day. Biochemistry data did not show a reduction of total cholesterol or GSLs in brain or liver after arimoclomol treatment up to 300 mg/kg/day.
Initial/ Re-submission	Arimoclomol dosing study in a mouse model of Niemann-Pick Type C disease/CRO-1202290013 **(Study 13)**	Survival, body weight, behavioral effects (rearing, tremor, gait analysis), and biochemistry endpoints evaluated in $Npc1^{-/-}$ ($Npc1^{nih}$) mice after arimoclomol treatment.	Arimoclomol at 30 mg/kg/day increased survival by +11.0%, while arimoclomol at 300 mg/kg/day increased survival by +7.0%. No clear treatment effect of arimoclomol on side and center rearing activity and behavioral endpoints. Increased glycosphingolipids in brain appear not supportive of the intended drug effect.
Initial/ Re-submission	Efficacy of a developmental compound in NPC1 knockout mice/CRO-1402050053 **(Study 53)**	Behavioral effects (rearing and gait analysis), body weight, survival, and biochemical parameters evaluated in $Npc1^{-/-}$ ($Npc1^{nih}$) mice after arimoclomol treatment.	No clear disease phenotype was observed in $Npc1^{-/-}$ mice in this study; healthy and diseased animals were indistinguishable.
Re-submission	A combination study of arimoclomol and miglustat in the $Npc1^{nih}$ mouse model: Survival and behavior/CRO-1707310132-DOC-2110260043 **(Study 43)**	Combined effect of arimoclomol and miglustat on survival and behavioral endpoints evaluated in the $Npc1^{-/-}$ ($Npc1^{nih}$) mice.	Arimoclomol at 30 mg/kg/day increased survival in $Npc1^{-/-}$ mice by 6.5%, miglustat at 600 mg/kg/day increased survival by 42.0%, while combination of arimoclomol and miglustat increased survival by 68.0%.
Re-submission	Effect of arimoclomol on survival and behavior of the $Npc1^{nmf/nmf}$ mouse model/CRO-1707310132-DOC-2201170045 **(Study 45)**	Survival, body weight, and behavioral endpoints (ataxia, motor coordination, balance, respiration, spontaneous movement, palpebral closure, tail position, pelvis position, piloerection) evaluated in $Npc1^{nmf/nmf}$ mice.	Arimoclomol at 100 mg/kg/day increased survival by 9.8%, and treatment at 500 mg/kg/day did not have any effect on survival. Arimoclomol at 100 mg/kg/day modestly delayed body weight loss. No clear dose-dependent effect of arimoclomol on behavioral endpoints.

NDA Submission	Nonclinical Study/Study Number	Study Design	Results
Re-submission	The effects of 100 mg/kg/day arimoclomol treatment on biochemical endpoints in Npc1 $^{nmf/nmf}$ mouse model/CRO-1707310132-DOC-2203180048 **(Study 48)**	Biochemical endpoints (total cholesterol and glycosphingolipids (GSLs), protein levels of NPC1, myelin basic protein (MBP), HSP70, [pSer326]HSF1, and selected genes evaluated in Npc1$^{nmf/nmf}$ mice.	Arimoclomol reduced cholesterol in liver but had no effect on cholesterol in brain. No clear effect of arimoclomol on GSLs in liver and brain and NPC1 protein in brain. Arimoclomol increased MBP levels in brain, but no effect on HSP70 and [pSer326]HSF1 in brain.

Source: Reviewer; prepared with Applicant's data from Applicant's Study Reports
Abbreviation: NPC, Niemann-Pick disease type C

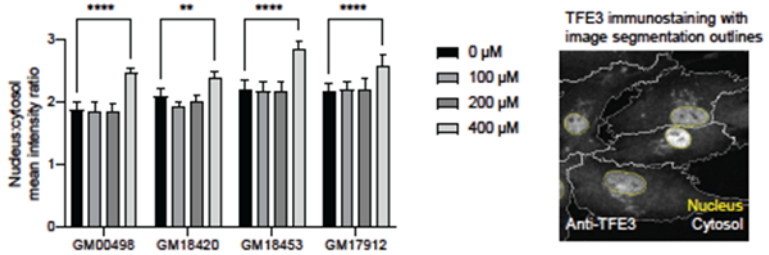
Data From Studies of Arimoclomol in Cultured Cells

Nuclear Translocation of TFE3 and TFEB in Cultured Cells

Because TFE3 and TFEB activation and subsequent nuclear localization is presumed to initiate the gene expression changes associated with CLEAR network activation, the Applicant evaluated the ability of arimoclomol to activate nuclear translocation of TFE3 and TFEB in cultured fibroblasts obtained from patients and healthy donors, and from HeLa cells. Treatment with arimoclomol was shown to increase the TFE3 nuclear: cytoplasmic ratio as measured by immunofluorescence; however, the dose-response appeared to exhibit a threshold effect at the highest concentration tested (400μM), as shown in Figure 5. There was also no difference in the overall magnitude of the response between patient-derived and wildtype fibroblasts, GM00498 (Figure 5). There was also no apparent effect of genotype on the extent of nuclear translocation measured (Table 10). A concentration of 400μM is 60-fold the clinical C_{max}. There was no evidence that lower concentrations induced TFE3/TFEB nuclear translocation.

Endoplasmic reticulum and lysosomal stress drive CLEAR gene expression via activation of TFE3/TFEB (Settembre et al. 2011; Martina et al. 2016; Raben and Puertollano 2016). This effect occurs under a broad array of stressors, including nutrient deprivation, infection, and mitochondrial damage. Indeed, in the same study, the Applicant demonstrated that starvation in WT fibroblasts (GM00969) and HeLa cells could induce a similar magnitude of effect on TFE3 and TFEB nuclear translocation as was observed with arimoclomol; this effect therefore appears to be nonspecific (Figure 6 versus Figure 5).

Figure 5. Immunostaining for TFE3 in WT and NPC Fibroblasts Treated with Arimoclomol



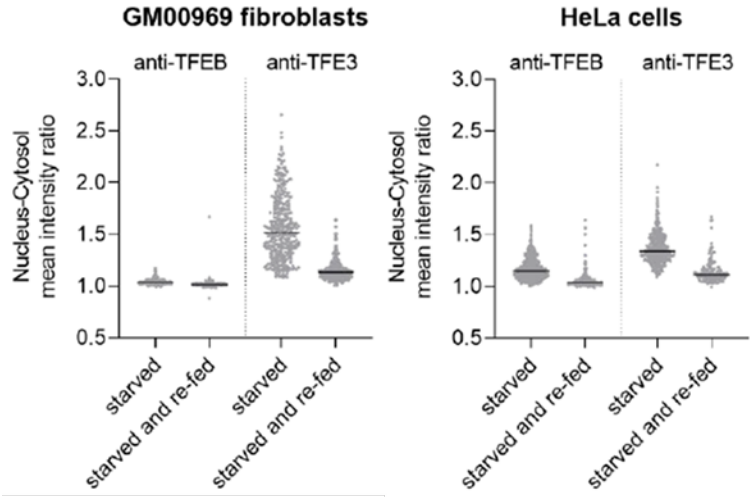
Source: Excerpted from the Applicant's submission – study report DOC-2110130040
Abbreviations: NPC, Niemann-Pick disease type C; TFE3, transcription factor E3; WT, wild type

Table 10. Genotypic Characteristics of the Fibroblast Cell Lines Used in Study Doc-2110130040

Cell line	Allele 1 DNA	Mutation type	Allele 1 Protein	Mutation group	Allele 2 DNA	Mutation type	Allele 2 Protein	Mutation group
GM00498	WT	n/a	WT	n/a	WT	n/a	WT	n/a
GM00969	WT	n/a	WT	n/a	WT	n/a	WT	n/a
GM17912	c.3019C>G	Missense	P1007A	Lyso	c.3107C>T	Missense	T1036M	Delayed
GM18420	c.3019C>G	Missense	P1007A	Lyso	g.IVS23+4delA	Splice	Null	Null
GM18453	c.3182T>C	Missense	I1061T	ER	c.3182T>C	Missense	I1061T	ER

Source: Excerpted from the Applicant's submission – study report DOC-2110130040
Abbreviation: ER, endoplasmic reticulum; n/a, not applicable; WT, wild type

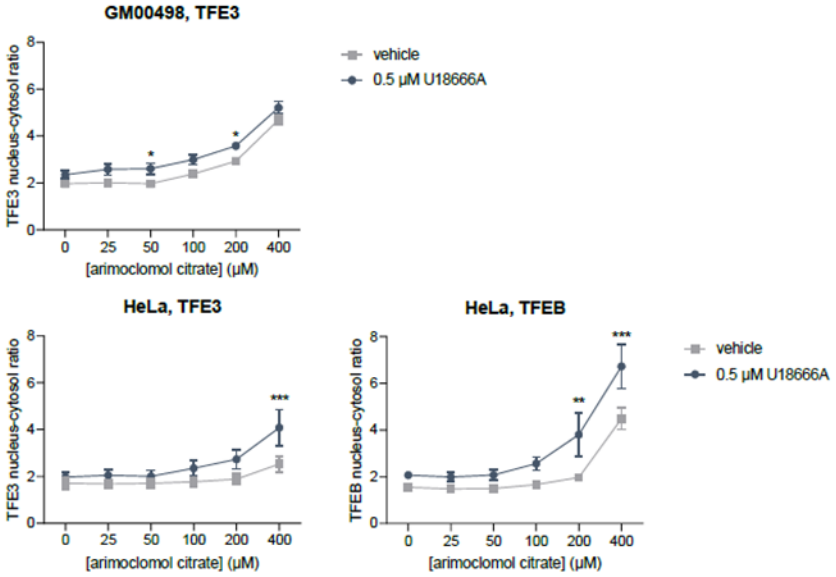
Figure 6. Effect of Starvation on TFEB and TFE3 Nuclear Translocation in WT Fibroblasts and HeLa Cells



Source: Excerpted from the Applicant's submission – study report DOC-2110130040
Abbreviations: TFE3, transcription factor E3; TFEB, transcription factor EB; WT, wild type

The Applicant also evaluated the effect of arimoclomol in WT and HeLa cells in the presence of the NPC1 inhibitor, U18666A. In non-transformed, wildtype fibroblasts, there was no clear effect on the magnitude of TFE3 nuclear translocation in the presence of U18666A; however, there did appear to be an increase in TFE3 nuclear translocation when HeLa cells were co-cultured with arimoclomol and U18666A. As shown in Figure 7, increased TFE3 and TFEB nuclear staining was observed at arimoclomol concentrations of >200µM (>30-fold the clinical C_{max}) when cultured in the presence of the NPC1 inhibitor, U18666A. The Applicant argues that this likely implies that cells deficient in NPC1 will respond to a greater extent than WT cells; however, based on the data from other studies, it does not appear that the magnitude of the effect was greater in NPC1-deficient cells, as shown in Figure 7.

Figure 7. TFE3 and TFEB Nuclear: Cytoplasmic Ratios in WT Fibroblasts and HeLa Cells Cultured with Arimoclomol and U-18666A

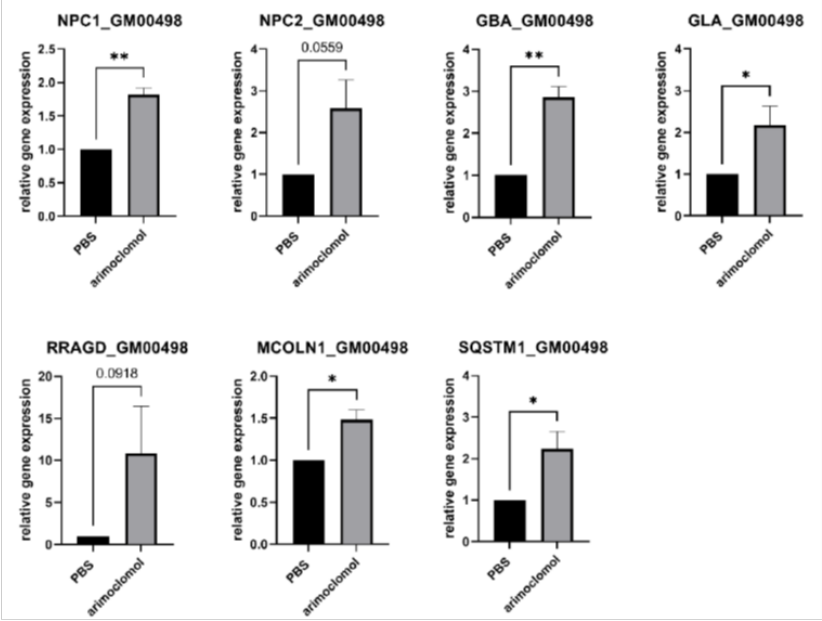


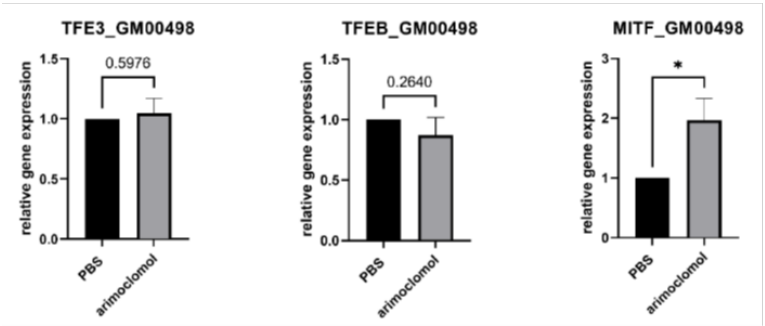
Source: Excerpted from the Applicant's submission – study report DOC-2204070049
Abbreviations: TFE3, transcription factor E3; TFEB, transcription factor EB; WT, wild type

Effect of Arimoclomol on Gene Expression in Cultured Cells

The Applicant hypothesizes that, because the CLEAR network is known to respond to stressors involving lysosomal and endosomal stress, upregulation of CLEAR genes may improve the underlying deficit associated with NPC. The Applicant demonstrated that in cultured cells (wildtype fibroblasts, NPC patient-derived fibroblasts, and HeLa cells), incubation with arimoclomol increased levels of TFE3 and TFEB nuclear translocation, binding of these transcription factors genes containing transcription factor E (TFE) binding sites, and upregulation of TFE-associated genes, including *NPC1* and *NPC2*. As shown in Figure 8, 400µM arimoclomol treatment for 5 days in cultured wildtype cells led to upregulation of mRNA for several genes, including *NPC1*, *NPC2*, *GBA*, *GLA*, *RRAGD*, *MCOLN1*, *SQSTM1*, and *MTIF*.

Figure 8. Effect of Arimoclomol on Target Gene mRNA Expression





Source: Excerpted from the Applicant's submission – study report DOC-2110140041
Abbreviations: NPC, Niemann-Pick disease type C; PBS, phosphate-buffered saline; TFE3, transcription factor E3; TFEB, transcription factor EB

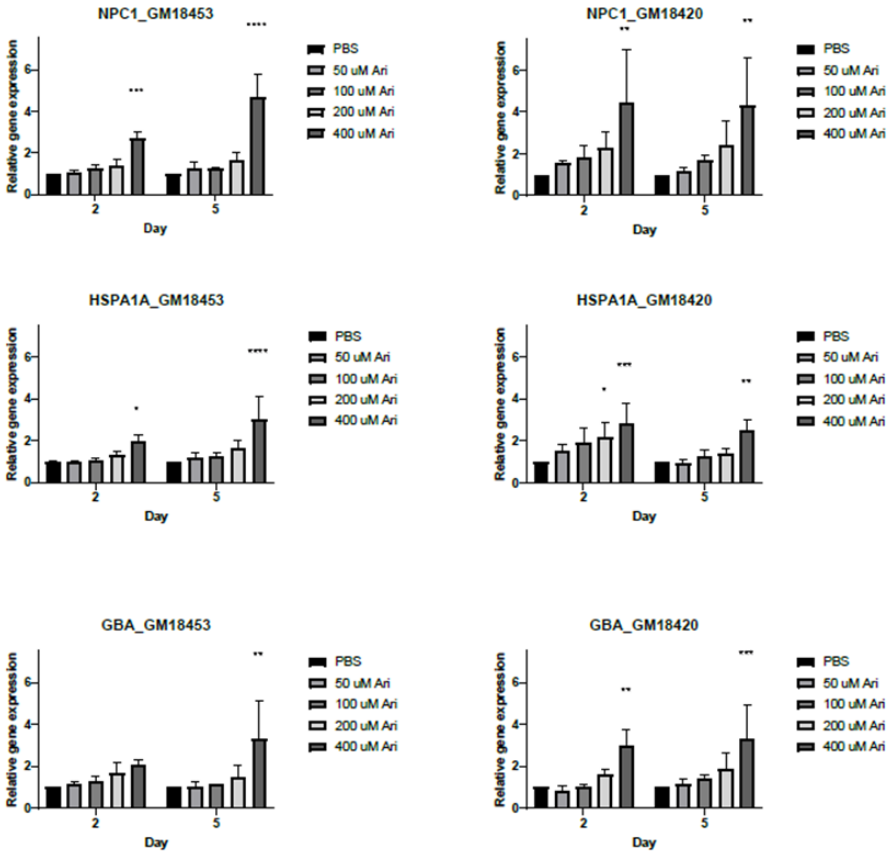
The Applicant conducted a similar study in two NPC patient-derived fibroblast cell lines (GM18420 and GM18453, Table 11). As shown in Figure 9, there was a dose-related increase in the expression of several genes, including *NPC1*, *NPC2*, *HSP1A1*, and *GBA*. The effects were only significant after treatment with 400μM arimoclomol for 5 days. As with the studies in wildtype cells, the magnitude of the effect on gene expression was generally very small, and there was no clear evidence that increased duration of exposure improved gene expression levels (Figure 9). As was shown in Study 40 (DOC-2110130040), there was also no evidence that genotype affected the magnitude of the response to arimoclomol in this study. There is also no information about whether the observed effects led to improvements in cellular function. The Applicant did not provide data on any marker of cellular health (oxygen consumption, ATP production, etc.), or viability. Given the high concentrations needed to elicit the observed effects (60-fold the clinical C_{max}), it is concerning that the effects described are nonspecific and may be occurring in the context of a significant impairment of cellular health or survival.

Table 11. Genotypic Characteristics of the Patient-Derived Fibroblasts Used in Study Doc-2110140042

Cell line	Allele 1 DNA	Mutation type	Allele 1 Protein	Mutation group	Allele 2 DNA	Mutation type	Allele 2 Protein	Mutation group
GM18453	c.3182T>C	Missense	I1061T	ER	c.3182T>C	Missense	I1061T	ER
GM18420	c.3019C>G	Missense	P1007A	Lyso	g.IVS23+4delA	Splice	Null	Null

Source: Excerpted from the Applicant's submission - study report DOC-2110140042
Abbreviation: ER, endoplasmic reticulum

Figure 9. Effect of Arimoclomol on the mRNA Levels of *NPC1*, *GBA*, and *HSP1A1*

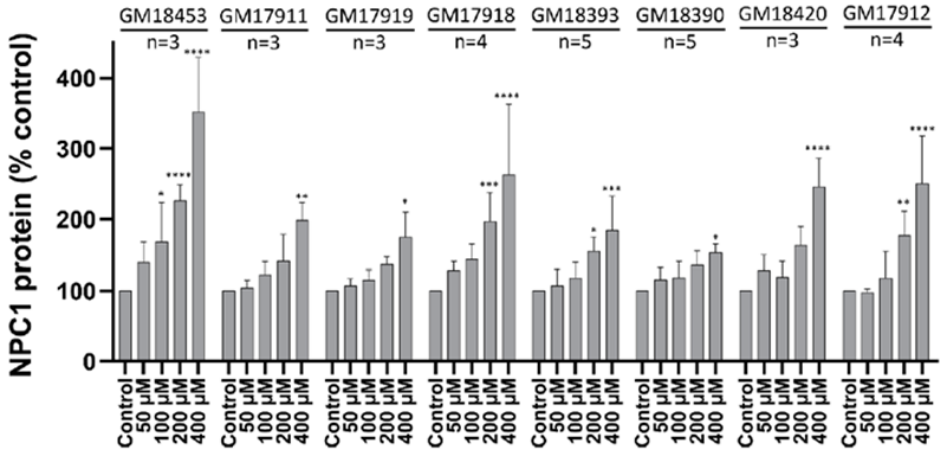


Source: Excerpted from the Applicant's submission - study report DOC-2110140042
Abbreviations: Ari, arimoclomol; PBS, phosphate-buffered saline

To characterize the effects of genotype on NPC1 protein levels and intracellular lysosomal lipid, the Applicant conducted a series of studies in cultured HeLa cells (human papillomavirus-transformed cervical cancer cell line), and in WT and NPC patient-derived fibroblasts.

Arimoclomol-induced upregulation of *NPC1* mRNA and protein expression in patient-derived fibroblasts carrying different mutations (Table 12). In eight cell lines derived from NPC patients, incubation with increasing concentrations of arimoclomol (50 to 400µM) increased NPC1 protein expression, which was generally dose-related and independent of genotype; the magnitude of the effect was very small and inconsistent; and it was largely only at the highest concentrations of arimoclomol (200 to 400µM) that the effect was statistically significant (Figure 10). These in vitro concentrations are 16-fold to 60-fold maximal plasma concentrations (~6.7µM) observed with the clinical doses. The clinical relevance of the in vitro findings at these high exposures is unclear.

Figure 10**. Effect of Arimoclomol on NPC1 Protein Level in NPC Patient Cell Lines Carrying Different Mutations**



Source: Excerpted from the Applicant's submission – study report DOC-2004170028
Abbreviation: NPC, Niemann-Pick disease type C

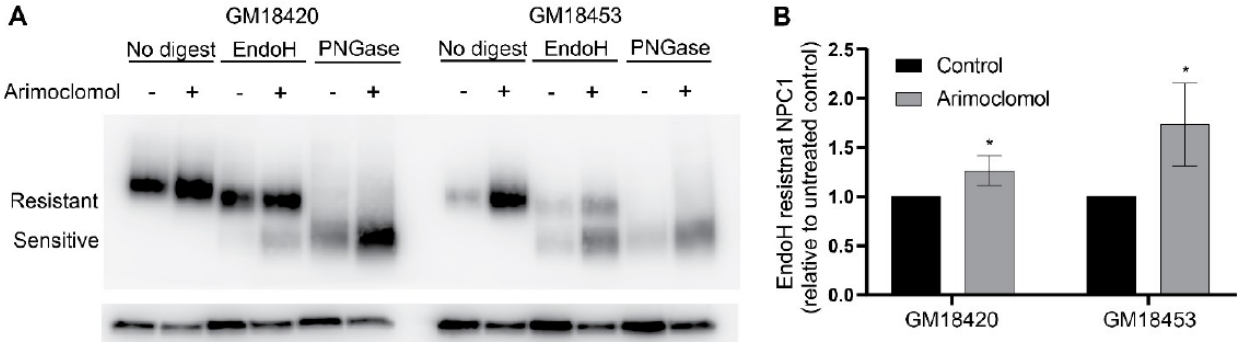
Table 12. Genotypic Characteristics of the Fibroblast Cell Lines Used in Study Doc-2004170028

Cell line	Allele 1 DNA	Mutation type	Allele 1 Protein	Mutation group	Allele 2 DNA	Mutation type	Allele 2 Protein	Mutation group
GM18453	c.3182T>C	Missense	I1061T	ER	c.3182T>C	Missense	I1061T	ER
GM17911	c.3182T>C	Missense	I1061T	ER	c.3107C>T	Missense	T1036M	Delayed
GM 17919	c.3182T>C	Missense	I1061T	ER	c.1210C>T	Missense	R404W	Other
GM17918	c.410C>T	Missense	T137M	Other	c.2336insT	Frameshift	Null	Null
GM18393	c.743G>T	Missense	G248V	Other	c.3425T>C	Missense	M1142T	ER
GM18390	c.724G>C	Missense	D242H	Other	c.2819C>T	Missense	S940L	Lyso
GM18420	c.3019C>G	Missense	P1007A	Lyso	g.IVS23+4delA	Splice	Null	Null
GM17912	c.3019C>G	Missense	P1007A	Lyso	c.3107C>T	Missense	T1036M	Delayed

Source: Excerpted from the Applicant's submission – study report DOC-2004170028
Abbreviation: ER, endoplasmic reticulum

It is also unclear what the functional significance of upregulating mutant NPC1 is in these cells. The Applicant attempted to address this question by showing increased escape from the endoplasmic reticulum using EndoH digestion, which cleaves mannose-rich residues in the endoplasmic reticulum. In two cell lines (GM14820, which is P1007A/Null, and GM18453, which is I1061T/I1061T), they state that treatment with arimoclomol led to a very small increase (1.3 to 1.8-fold, Figure 11) in NPC1 Golgi trafficking response to arimoclomol treatment at 400µM for 5 days; however, the increase was so small that it cannot be clearly differentiated from experimental error resulting from variables like minor differences in sample loading; electrophoretic artifacts; effects of digitization and image analysis, etc. They also neglected to show that the protein localized correctly to the lysosome, that it elicited meaningful downstream effects, and that the cells were generally healthy. Given the very high levels of drug needed to elicit this effect, it appears to be a nonspecific, adaptive effect, rather than a selective PD response to treatment.

Figure 11. Effect of Arimoclomol on NPC1 EndoH Sensitivity in Cultured Patient-Derived Cells



Source: Excerpted from the Applicant's submission – study report DOC-2004170028
Abbreviation: PMGase, peptide-N-glycosidase

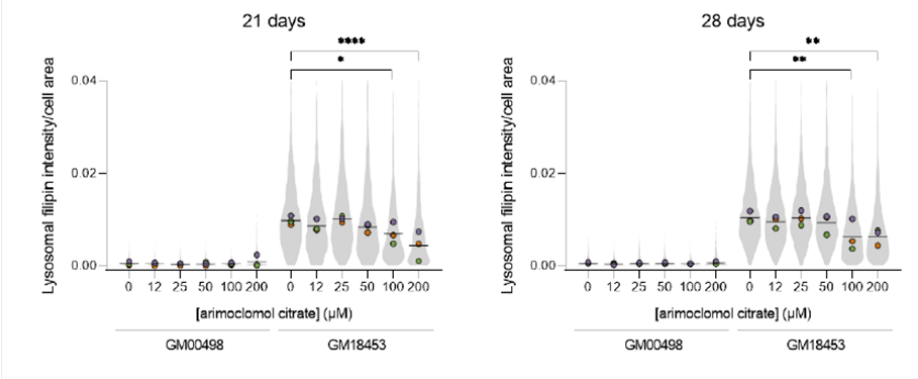
The Applicant also evaluated the effects of arimoclomol on filipin staining in WT and NPC patient-derived fibroblasts. Filipin staining is a fluorescent dye that is used to quantify the amount of unesterified cholesterol in cells. As shown in Figure 12, there was a very modest, largely non-dose-related reduction in filipin staining at concentrations of 100 to 200µM, which is 15 to 30-fold the clinical C_{max}. The peak effect occurred at 21 days, and there was no significant effect of duration on the magnitude of the effect thereafter. Because the Applicant only evaluated one cell line that is homozygous for the I1061T mutation, there is no information about whether genotype affects the outcome. That these very small effects are only observed at concentrations that are physiologically implausible casts doubt on the physiological relevance of this effect. In the absence of data about overall cellular health, it is impossible to exclude the effects of toxicity from this effect. Filipin staining is also technically challenging due to photo-lability, and it is unclear what measures were considered for potential loss of signal with storage and/or light exposure in the study. Given the small magnitude of the effect, it is possible that storage or light exposure could have affected the outcome of the study.

Table 13. Genotypic Characteristics of the Cell Lines Used in Study Doc-2112170044

Cell line	Allele 1 DNA	Mutation type	Allele 1 Protein	Mutation group	Allele 2 DNA	Mutation type	Allele 2 Protein	Mutation group
GM00498	WT	n/a	WT	n/a	WT	n/a	WT	n/a
GM18453	c.3182T>C	Missense	I1061T	ER	c.3182T>C	Missense	I1061T	ER

Source: Excerpted from the Applicant's submission – study report DOC-2112170044
Abbreviations: ER, endoplasmic reticulum; n/a, not applicable; WT, wild type

Figure 12. Filipin Staining Intensity in WT (GM00498) and NPC Patient-Derived (GM18453) Fibroblasts



Source: Excerpted from the Applicant's submission – study report DOC-2112170044
Abbreviations: NPC, Niemann-Pick disease type C; WT, wild type

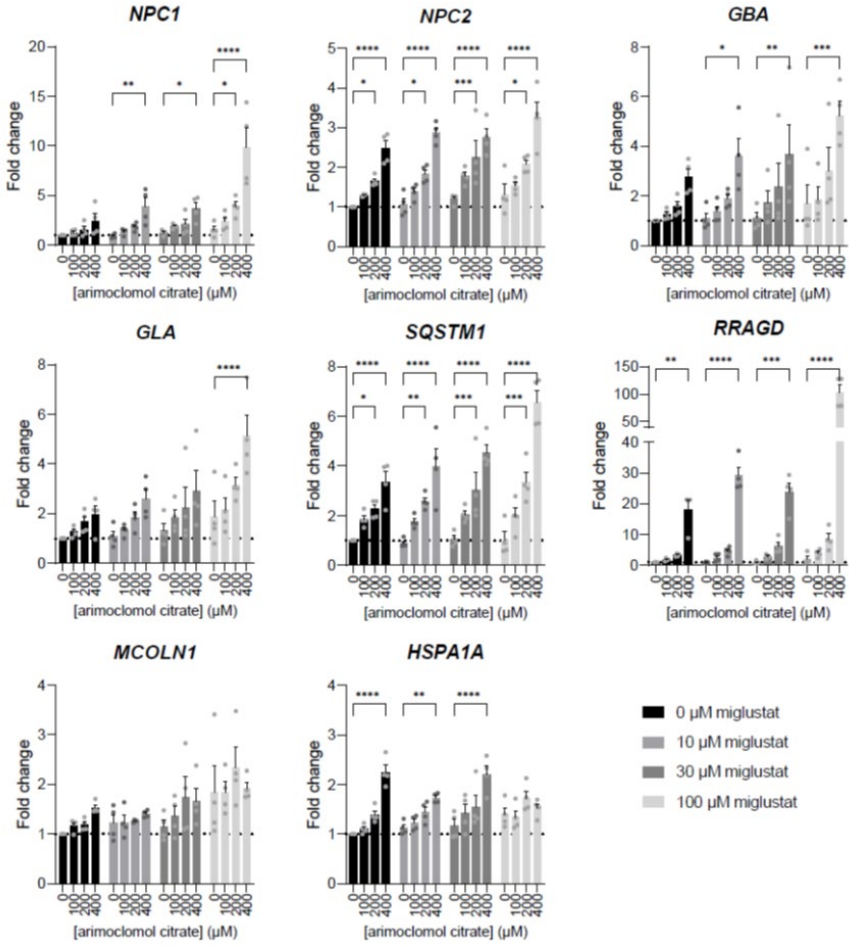
In conclusion, data from arimoclomol monotherapy studies in cultured wildtype and patient-derived fibroblasts suggest that:

- The molecular target of arimoclomol is unknown.
- The Applicant proposes that arimoclomol activates the CLEAR network, which is a ubiquitous and nonspecific adaptive pathway that is known to become activated by several stressors.
- The effects of arimoclomol on TFE3/TFEB nuclear translocation and target gene expression were only observed at markedly supratherapeutic concentrations (up to 60-fold the clinical C_{max}) and the observed responses were numerically very small.
- Arimoclomol reduced the level of stored lipid in patient-derived cells; however, the effect was only observed at exposures that are markedly above the clinical range (30 to 60-fold the clinical C_{max}) and the magnitude of the response was extremely small.
- CLEAR gene expression is an adaptive response to stress. In the absence of information on cellular health/cytotoxicity, the responses are indistinguishable from a nonspecific, adaptive response to toxicity.
- The Applicant did not assess cellular health (e.g., oxygen consumption or ATP production) or viability.

Data From Studies of Arimoclomol Plus Miglustat in Cultured Cells

The Applicant investigated the possible additive effects of arimoclomol and miglustat treatment in vitro, by measuring transcriptional upregulation of lysosomal genes from the CLEAR network including *NPC1*, *NPC2*, *GBA*, *GLA*, *RRAGD*, *SQSTM1* and *HSPA1A* (encodes HSP70) in cultured human fibroblasts from an NPC patient (GM18453) with homozygous I1061T mutation. Arimoclomol increased the expression of CLEAR genes *NPC1*, *NPC2*, *GBA*, *GLA*, *RRAGD*, *SQSTM1*, and *HSPA1A* both in the presence and absence of miglustat. Importantly, there was enhanced expression of CLEAR network genes at higher concentrations of both drugs in combination when compared to arimoclomol and miglustat treatment alone. The additive effect of arimoclomol and miglustat generally only reached statistical significance at concentrations of 200 to 400µM arimoclomol in combination with 100µM miglustat (Figure 13).

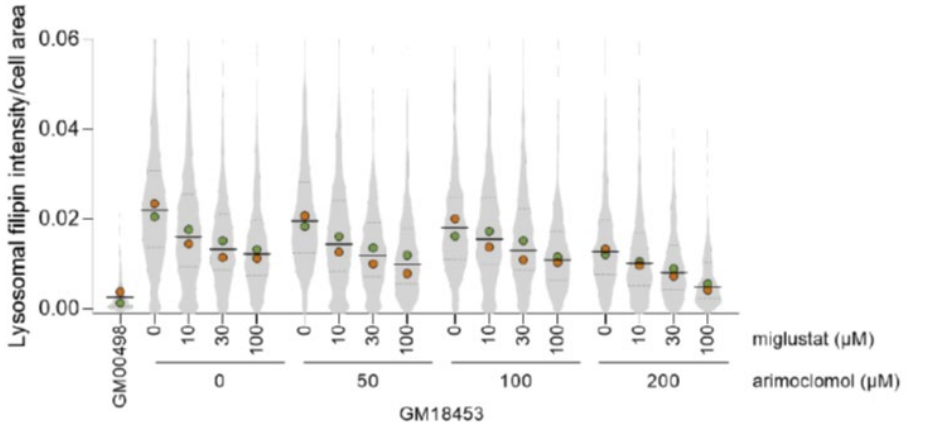
Figure 13. Expression of Selected CLEAR Network Genes and HSPA1A After Combination Treatment with Arimoclomol and Miglustat, Grouped by Miglustat Concentration



Source: Excerpted from Applicant's Study Report DOC-2201240047
Abbreviations: HSP, heat shock protein

The Applicant also evaluated the additive effects of arimoclomol and miglustat combination treatment on filipin staining in WT and NPC patient-derived fibroblasts (GM18453). Cells were cultured for 7 and 14 days at concentrations of 0, 50, 100, or 200μM arimoclomol and 0, 10, 30, or 100μM miglustat. Unesterified (free) cholesterol was analyzed by filipin staining. As shown in Figure 14 and Table 14, there was reduced filipin staining intensity with increasing concentrations of arimoclomol and miglustat. The combination reduced the accumulation of unesterified cholesterol to a degree that is greater than that observed with either agent alone. Most of the effect appeared to be attributable to miglustat; however, the results suggest an additive effect of combining arimoclomol and miglustat treatment on the accumulation of unesterified cholesterol in cultured human fibroblasts derived from NPC patients. There is no clear effect with arimoclomol alone at 7 days (data not shown); it is not until 14 days that there is a significant reduction observed and only at the high dose. Similarly, for miglustat alone, there is no clear effect at 7 days (data not shown), but at 14 days, there is a similar effect to arimoclomol alone. The effect appears to be additive at both 7 and 14 days; however, there is no information about cellular viability or health in these cultures.

Figure 14. Lysosomal Filipin Intensity After 14 Days of Treatment with Arimoclomol and Miglustat



Source: Excerpted from the Applicant's submission – study report DOC-2201240046

Table 14. Filipin Intensity as Percentage of Vehicle-Treated Control, 14 Days Treatment

14 days treatment		Miglustat			
		0 μM	10 μM	30 μM	100 μM
Arimoclomol	0 μM	100%	73%	61%	56%
	50 μM	89%	65%	54%	45%
	100 μM	82%	71%	59%	50%
	200 μM	58%	46%	37%	22%

Source: Excerpted from the Applicant's submission – study report DOC-2201240046

In conclusion, there appears to be some evidence that miglustat may augment the effects of arimoclomol; however, the data are weak for the following reasons:

- The effects on cholesterol levels were generally only observed at the highest concentrations of both miglustat and arimoclomol. The Applicant also did not detail the methodology sufficiently to rule out that effects of storage or light exposure might have affected the fluorescence quantification in this study.
- The magnitudes of the effects were generally small and of uncertain physiological relevance given the supraphysiological concentrations used (up to 60-fold the clinical C_{max} for arimoclomol and up to 18-fold the clinical C_{max} for miglustat).
- No data were presented on cellular viability or health (e.g., ATP production) that would aid in differentiating the effects of treatment from the effects of toxicity.

Animal Models of NPC: Effects of Arimoclomol With and Without Miglustat

The Applicant has conducted multiple studies in animals to evaluate the effects of arimoclomol on disease progression. The endpoints that were evaluated included survival, automated gait analysis, and rotarod performance, which measures neurobehavioral aspects related to strength, mobility, and balance. Ataxia is one of the early features of NPC in the two murine models evaluated, so the Applicant

evaluated various motor functions related to gait and rearing. These studies included computerized gait analysis systems (CatWalk) which uses a high-speed camera to measure aspects of the animal's gait as it traverses a glass plate. Rotarod performance evaluates the ability of the animal to traverse a revolving rod and the output is measured as time to fall, distance traveled, and the speed at fall, which is the speed of rotation at which the animal fell from the rod. In a subset of the studies, the Applicant also measured several lipid-related biochemical analytes and gene expression changes related to the selected CLEAR network genes that were evaluated in cultured cells.

In the original NDA submission, the Applicant conducted three in vivo studies (CRO-1211210031 [Designated as "Study 31"], CRO-1402050053 [Study 53], and CRO-1202290013 [Study 13]) in $Npc1^{-/-}$ mice. In the resubmission, the Applicant also evaluated the effect of arimoclomol in $NPC1^{nmf/nmf}$ mice. In both sets of studies, the Applicant administered the drug in the drinking water, and in both models, treatment was initiated pre-symptomatically, at 3 weeks of age and mice continued to receive treatment for 5 weeks (males), or until they reached the humane endpoint (females).

The Applicant conducted six studies in NPC1 mice, four in the $NPC1^{-/-}$ mouse model, and two in the $NPC1^{nmf/nmf}$ model. Except for one study ("Study 53" described below), none of the reports stated that the animals were randomized to treatment, and we have no information about potential baseline imbalances in disease severity between the groups. Except for Studies 43 and 45, we do not know if the assessors who made the determinations about whether the animal had met the humane endpoint were blinded to the treatment group. Because the determination that an animal met the humane endpoint determines the animal's age at euthanasia, this can confound the interpretation of survival. Also, in most cases, the animal numbers per group were very small. In general, survival was assessed in four to eight animals per group. Small baseline imbalances in disease severity, bias in interpreting disease progression, and small animal numbers per group can make overall interpretation of survival very difficult.

Table 15. Study Description of Survival Data

Study No.	**CRO-1202290013 (Study 13)**	**CRO-1402050053 (Study 53)**	**CRO-1707310132-DOC-2110260043 (Study 43)**	**CRO-1707310132-DOC-2201170045 (Study 45)**
Test site	Oxford University	QPS Austria	Oxford University	Oxford University
Mouse Strain	$Npc1^{-/-}$	$Npc1^{-/-}$	$Npc1^{-/-}$	$NPC1^{nmf/nmf}$
Group size	4F/group	8F/group	6-8F/group	4-7F/group
Animals randomized to treatment	No	Yes	No	No
Assessors blinded to treatment	No	No	Yes	Yes
Dose levels (mg/kg/day)	30, 300	1, 3, 10, 30	30 (arimoclomol); 600 (miglustat)	10, 50, 100 or 500

Study No.	CRO-1202290013 (Study 13)	CRO-1402050053 (Study 53)	CRO-1707310132-DOC-2110260043 (Study 43)	CRO-1707310132-DOC-2201170045 (Study 45)
Survival	untreated - 78 days; 30 mg/kg - 86.5 days (11.0%); 300 mg/kg - 83.5 days (7.0%)	untreated (drinking water) - 72.3 days; untreated (oral gavage) - 74.4 days. Arimoclomol treatment with either compound concentration or route did not alter survival rate in study	untreated - 84.5 days; arimoclomol - 90 days (+6.5%); miglustat - 120 days (+42.0%); arimoclomol + miglustat - 143 days (+68.0%)	untreated - 16.7 weeks; 10 mg/kg - 16.9 weeks (+1.3%); 50 mg/kg - 17.3 weeks (+3.8%); 100 mg/kg - 18.3 weeks (+9.8%); 500 mg/kg - 16.7 weeks (0%)

Source: Reviewer; prepared with Applicant's data from Applicant's Study Reports
Abbreviation: F, female

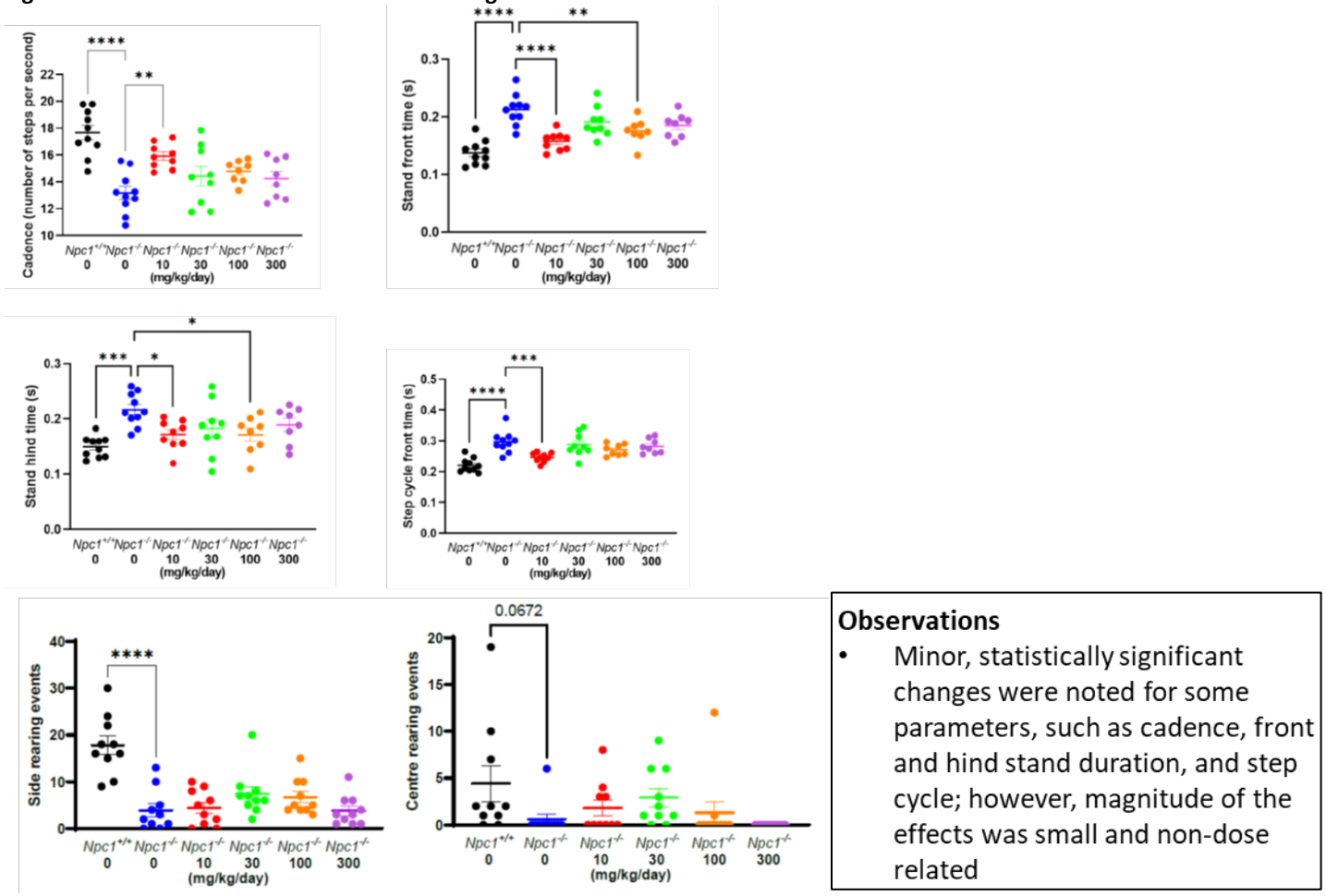
As discussed in detail below, the effects of arimoclomol in these models were small in magnitude, inconsistent, and/or lacked an effect of dose. The Applicant evaluated effects on neurobehavioral parameters (rotarod, gait, and rearing), and survival in some studies; however, the effects generally occurred at the lowest doses and showed no effect at higher doses. In at least one instance, effects on survival were not replicated in a second study conducted at the same dose level. The data were very difficult to interpret because the Applicant administered the drug in the drinking water and did not measure water consumption at most of the dose levels at which the drug was administered. They also did not obtain PK in any study; therefore, neither the dose administered, nor the resulting exposure could be estimated. Whether the lack of an apparent dose-effect in animals is due to a failure to deliver the drug, or to toxicity secondary to high arimoclomol exposure levels, is therefore unclear. The results of these studies, and the caveats regarding overall study interpretation, are discussed below.

Study 31: Effect of Arimoclomol in NPC1$^{-/-}$ Mice on Gait and Rearing

The purpose of Study 31 was to evaluate the effects of arimoclomol on behavior and rearing when arimoclomol was administered in the drinking water at doses of 0, 30, 100, or 300 mg/kg/day from approximately 21 days of age until 54 days of age. The Applicant states that the NPC1$^{-/-}$ mouse model develops symptoms of ataxia and tremor at 6 weeks of age and typically die by 11 weeks of age; however, despite initiating treatment pre-symptomatically, there were no dose-related effects on rearing, posture, or gait. Minor, statistically significant changes were noted for some parameters, such as cadence, front and hind stand duration, and step cycle; however, magnitude of the effects was small and non-dose related (Figure 15). The Applicant did not evaluate the effect of treatment on survival in this study.

Biochemistry data collected from male mice during Week 8 of treatment did not show a reduction in total cholesterol or GSLs in the brain or liver after arimoclomol treatment. Neither the volume of water consumed, the stability of the test article in drinking water, nor the arimoclomol blood levels attained in this study were measured. Therefore, it is difficult to interpret these studies because the route of administration may have affected water consumption (and the administered dose), particularly at the highest dose levels.

Figure 15. Selected Gait Parameters and Rearing Events Measured in Arimoclomol-Treated NPC1$^{-/-}$ Mice



Source: Excerpted from the Applicant's submission - study report CRO-1211210031
Abbreviations: NPC, Niemann-Pick disease type C; WT, wild type

Study 13: Effects of Arimoclomol on Survival, Motor Function, and Biochemical Endpoints

The Applicant conducted another study in NPC1$^{-/-}$ mice, Study 13 (CRO-1202290013), to evaluate the effects of arimoclomol on survival, biochemical endpoints, gait, and motor function. In Study 13, NPC1$^{-/-}$ mice were treated with doses of 0, 30, or 300 mg/kg/day in drinking water

between the ages of 3 weeks until termination at 13 weeks, or until they met the humane endpoint. Behavioral and motor evaluations were performed using three behavioral tests (rearing, tremor, gait analysis). Rearing and tremor were observed at 6, 8, and 10 weeks of age (3, 5, and 7 weeks of treatment). They also evaluated rearing at 4, 12, and 14 weeks of age for WT controls, 4, 12, and 13 weeks of age at the 30 mg/kg/day dose level, and 4 and 11 weeks of age at the 300 mg/kg dose level. Tissues were collected from male mice at 5 weeks for measurement of glycolipids in the cerebellum, forebrain, and liver. Females were allowed to continue until they reached the humane endpoint. There were no effects on body weight (Figure 16). A minor effect on survival was observed at 30 mg/kg/day; however, the effect was not dose-related, as survival at 300 mg/kg/day was reduced relative to that of the 30 mg/kg/day treatment arm (Figure 16). Although there was a small rightward shift in survival of the 300 mg/kg dose level relative to the untreated controls, it is very difficult to interpret this because this analysis was based on data from only 5 animals per group. The lack of information about PK and water consumption further complicates the interpretation of these data because it is not possible to differentiate drug effects from statistical variability, failure to receive the intended dose, or whether the apparently reduced survival in high-dose animals was secondary to drug-related toxicity. Moreover, as described below, this effect on survival was not replicated in another study, Study 53 (CRO-1402050053) (Figure 18), conducted at doses of up to 30 mg/kg/day/kg/day.

Figure 16. Body Weight and Survival Measured in Arimoclomol-Treated NPC1$^{-/-}$ Mice

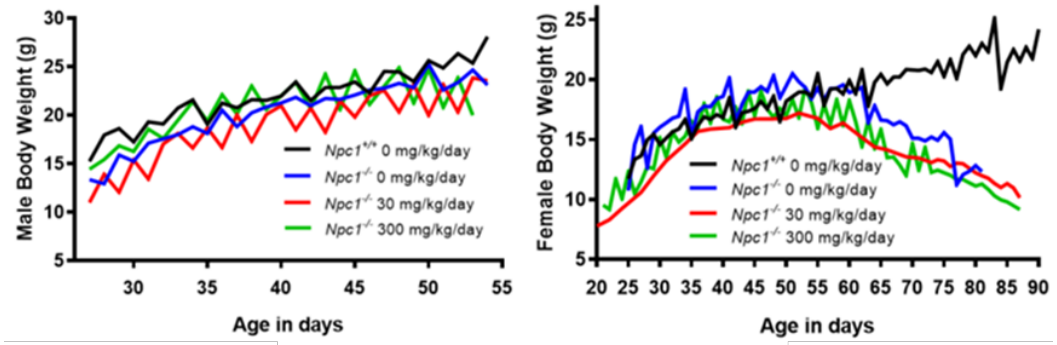
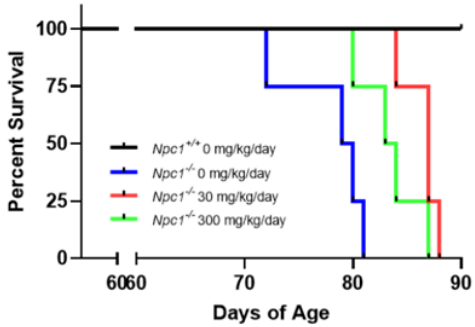


Figure 8-3 Survival in Female Mice



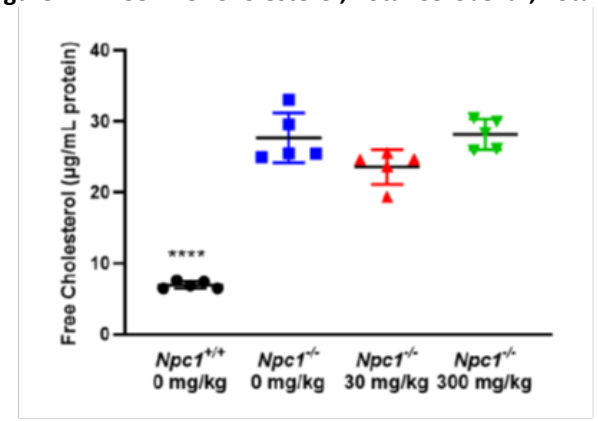
Observations

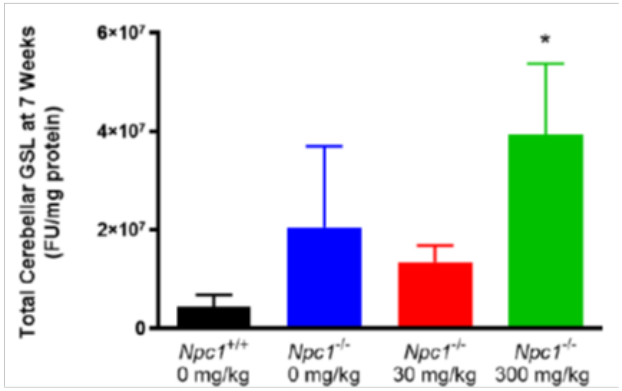
- No differences in BW in male KO (to Week 55), with weight loss in female KO mice after Week 65
- Decreased survival vs WT in KO
- Modest increases in survival with arimoclomol, trend at both doses, more notable at 30 vs 300 mg/kg/day

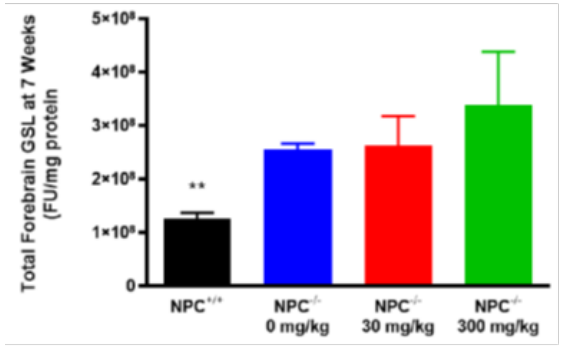
Source: Excerpted from the Applicant's submission - study report CRO-1202290013
Abbreviations: BW, bodyweight; KO, knockout; NPC, Niemann-Pick disease type C; WT, wild type

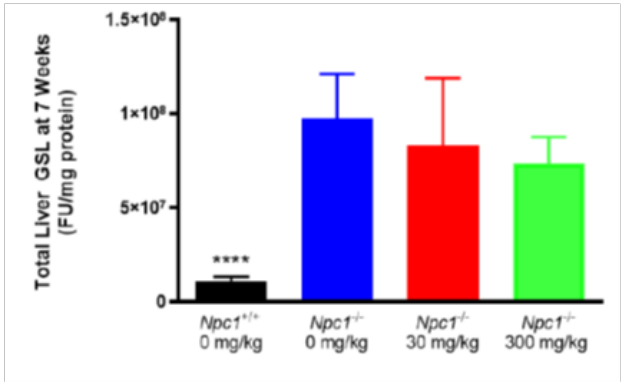
There were no statistically significant effects on mobility. The Applicant also evaluated cholesterol and glycosphingolipids in male animals euthanized on Day 54. There was a net increase in brain cholesterol and apparent increase on GSLs in the brains of knockout mice. There was no clear effect of treatment on cholesterol and GSLs; however, there was a minor and non-significant reduction in unesterified cholesterol liver at 30 mg/kg/day in the liver at 7 weeks of age; however, the effect was not dose-related, as higher unesterified cholesterol levels were observed at 300 mg/kg/day. An apparent increase in cerebellar GSLs was observed in the high dose level (Figure 17), which is unexpected, given the proposed MOA. There was a minor dose-related reduction in total glycosphingolipids in the liver at 7 weeks of age; however, statistical significance was not achieved.

Figure 17. Free Liver Cholesterol, Total Cerebellar, Total Forebrain and Liver GSLs Measured in Arimoclomol-Treated NPC1$^{-/-}$ Mice









Observations

- Increased liver free cholesterol and GSL, also increased liver GSL in KO animals
- Arimoclomol increased brain GSL and slightly decreased liver GSL at the highest dose

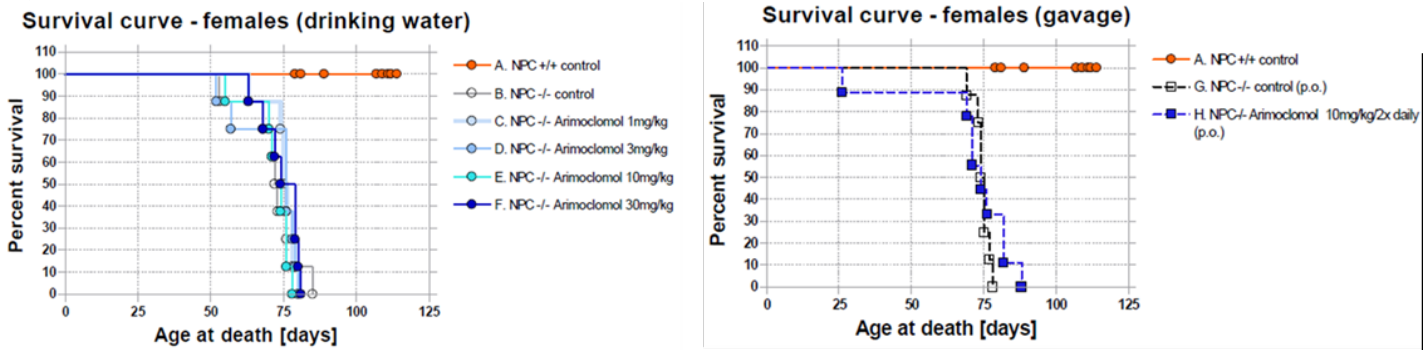
Source: Excerpted from the Applicant's submission - study report CRO-1202290013
Abbreviations: GSL, Glycosphingolipid; KO, knockout; NPC, Niemann-Pick disease type C

Study 53: Effect of Arimoclomol on Survival, Motor Function, and Biochemical Endpoints

The Applicant conducted another study, Study 53 (CRO-1402050053), in NPC1$^{-/-}$ mice to confirm the effects of Study 13. This study was conducted at a different facility. In Study 53, arimoclomol was administered to 8 mice per sex at doses of 0, 1, 3, 10, and 30 mg/kg/day in the drinking water, or by oral gavage at doses of 0 and 10 mg/kg/day. Males were euthanized for collection of blood and tissues (liver) after 4 weeks of treatment. Females remained on study until the terminal endpoint. Animals underwent extensive motor and behavioral testing, and water consumption was evaluated for estimation of delivered dose. Although water consumption did not appear to be affected by the presence of drug at concentrations sufficient to deliver a 30 mg/kg daily dose, total water consumption declined in all treated groups compared with WT controls, particularly during weeks 8 to 11, which may be consistent with impaired motor function.

There were no treatment-related effects on any endpoint evaluated. Importantly, the apparent effect on survival that had been observed at 30 mg/kg in Study CRO-1202290013, was not replicated in this study.

Figure 18. Effect of Arimoclomol on Survival in NPC1$^{-/-}$ Mice



Observations

- Decreased survival in the KO mice.
- No effect of arimoclomol on survival at any dose studied.

Source: Excerpted from the Applicant's submission - study report CRO-1402050053

In conclusion, there were no clear or consistent effects of treatment on any endpoint evaluated in the $NPC1^{-/-}$ mice when arimoclomol was administered in the drinking water.

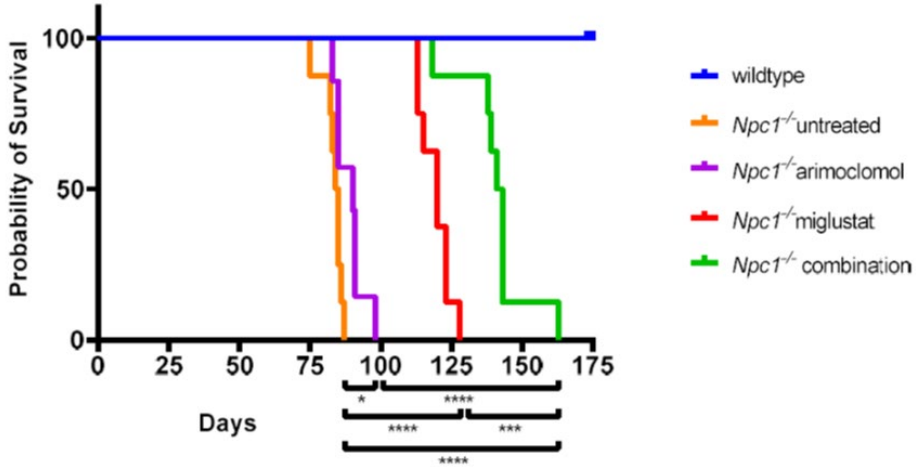
- There was no consistent effect of treatment on survival at any dose level, despite initiation of treatment during the period while the animals were still presymptomatic.
- There was no clear effect on parenchymal (liver or brain) GSL or cholesterol accumulation in treated animals; however, it is unclear whether the intended doses were administered over the dose range.
- Apparent effects on motor function in treated animals were minimal in magnitude, inconsistent, and not dose related.
- Interpretation of these data is limited by the lack of data on the delivered dose and lack of information about the resulting pharmacokinetic exposures in treated animals.

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

The Applicant also evaluated the combined effect of arimoclomol and miglustat on survival, body weight, and neurobehavioral endpoints including motor function, high frequency tremor, and gait in $Npc1^{-/-}$ mice. Arimoclomol was administered in the drinking water at concentrations sufficient (based on published drinking water volumes) to deliver a dose of 30 mg/kg/day, and miglustat at 600 mg/kg/day was administered in feed.

The untreated wildtype control mice ($Npc1^{+/+}$) survived for 84.5 days, while the arimoclomol-treated mice survived to 90 days (+6.5% compared to untreated control). The miglustat-treated mice improved survival to 120 days (+42.0% compared to untreated control), demonstrating a role for miglustat in improving survival. Combination of arimoclomol and miglustat further improved survival to 142 days (+68.0% compared to untreated control) (Figure 19) demonstrating that while arimoclomol had a numerically marginal and statistically significant but small effect on survival, the effect of miglustat was numerically larger and statistically stronger and the combination treatment of arimoclomol and miglustat produced an additive effect on survival.

Figure 19. Effects of Therapies on Survival

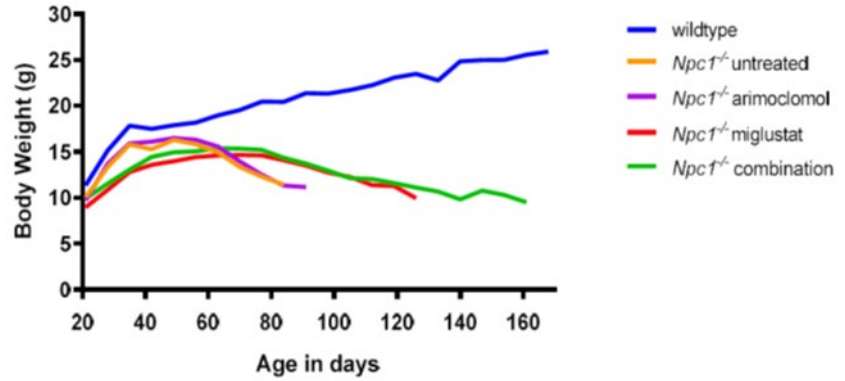


	Npc1$^{-/-}$ untreated	*Npc1*$^{-/-}$ arimoclomol	*Npc1*$^{-/-}$ miglustat	*Npc1*$^{-/-}$ combination
Median survival (Days)	84.5	90	120	142
% increase in survival compared to untreated	-	6.5	42	68
p-value compared to untreated	-	0.0205	<0.0001	<0.0001
p-value compared to combination	<0.0001	<0.0001	0.0007	-

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

The body weight of Npc1$^{-/-}$ mice was lower than that of wildtype mice (Npc1$^{+/+}$) at the start of the study and throughout disease development, and there was progressive body weight gain in wildtype mice throughout the study. The body weight of untreated Npc1$^{-/-}$ mice and arimoclomol-treated Npc1$^{-/-}$ mice plateaued around day 60, and then progressively declined by day 80; however, miglustat-treated mice and mice treated with combination of arimoclomol and miglustat exhibited delayed onset of weight loss before a gradual decline after day 120 (Figure 20). This supports a potential additive effect of the combination of arimoclomol and miglustat in delaying the loss of body weight.

Figure 20. Effects of Therapies on Body Weight

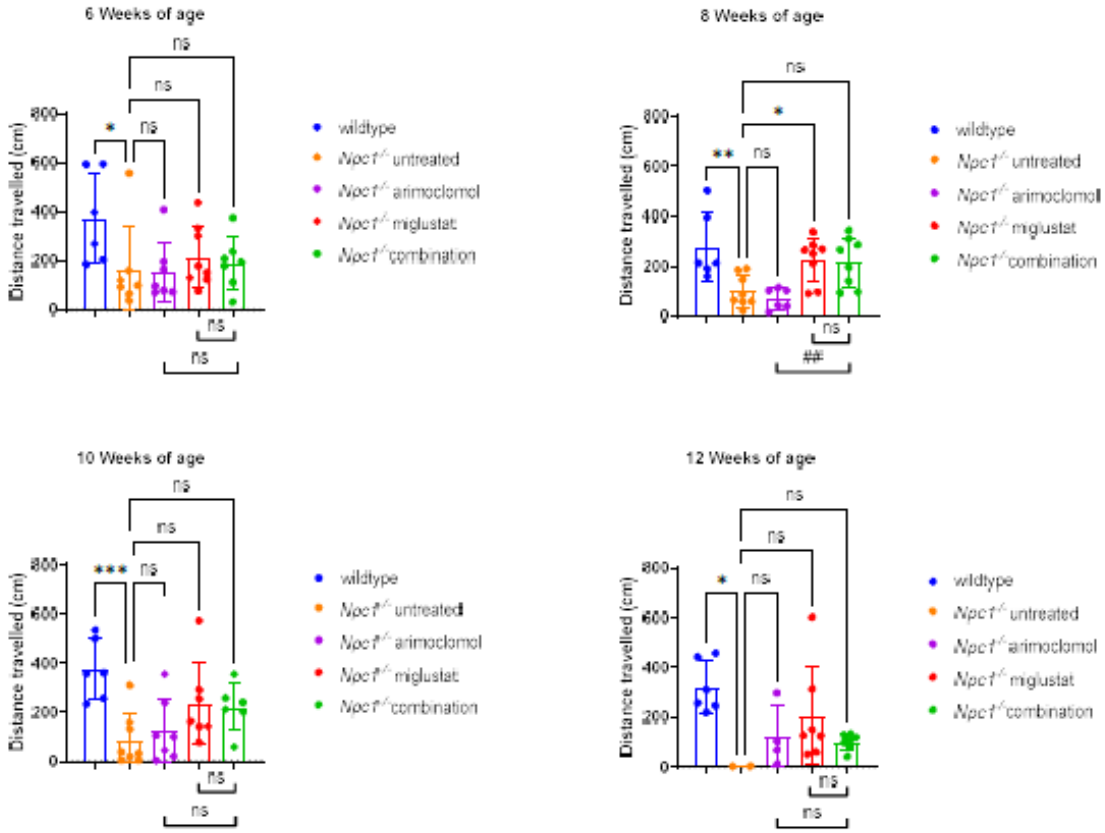


Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Progressive motor dysfunction is a characteristic of Npc1$^{-/-}$ mice. Therefore, motor function was measured in three rotarod parameters: distance travelled (cm), latency to fall (seconds) and speed at fall (rpm) in Npc1$^{-/-}$ mice. Treatment with arimoclomol alone had no effect on any of the motor function parameters, while miglustat alone and the combination of arimoclomol and miglustat improved motor

function in a similar manner in all of the three rotarod parameters of travelling distance (Figure 21), latency to fall (Figure 22), and speed at fall (Figure 23) in $Npc1^{-/-}$ mice. In mice treated with miglustat, but not in mice treated with arimoclomol or the combination of arimoclomol plus miglustat, there was a transient improvement at 8 weeks in the distance traveled on the rotarod. This is consistent with the effect of miglustat that was observed on side rearing (Figure 24). Unlike the effect on rotarod performance, the effect on side rearing appeared to show evidence of additivity (albeit very modest) with arimoclomol, and the duration of the effect appeared to be slightly more durable.

Figure 21. Effects of Therapies on Traveling Distance (Rotarod)

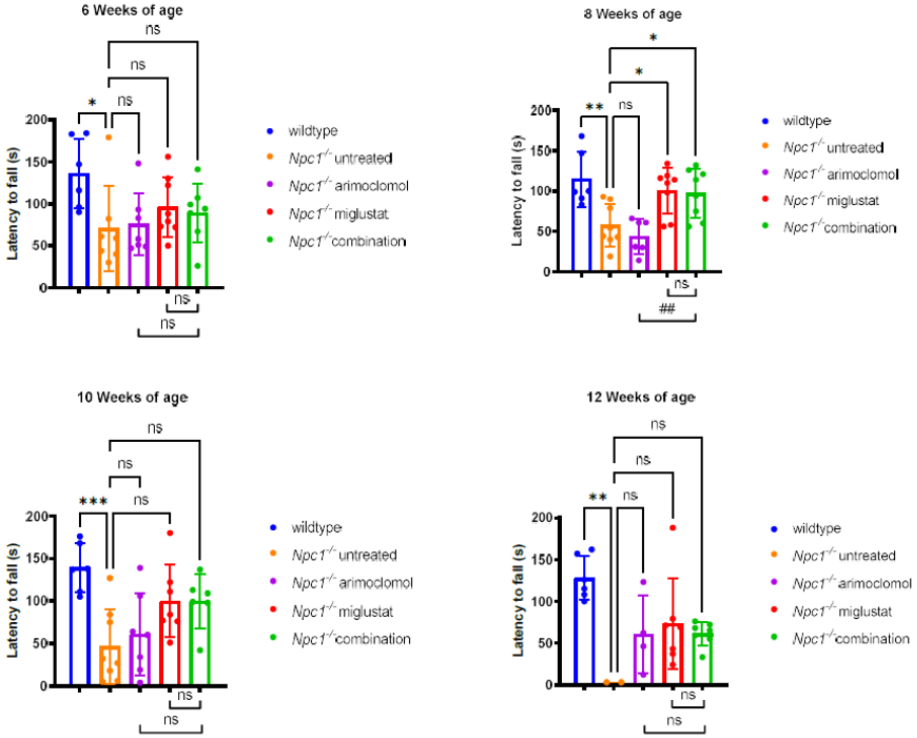


Observations

- No effect of arimoclomol at any age
- Miglustat improved distance traveled at 8 Weeks of age

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Figure 22. Effects of Therapies on Latency to Fall (Rotarod)

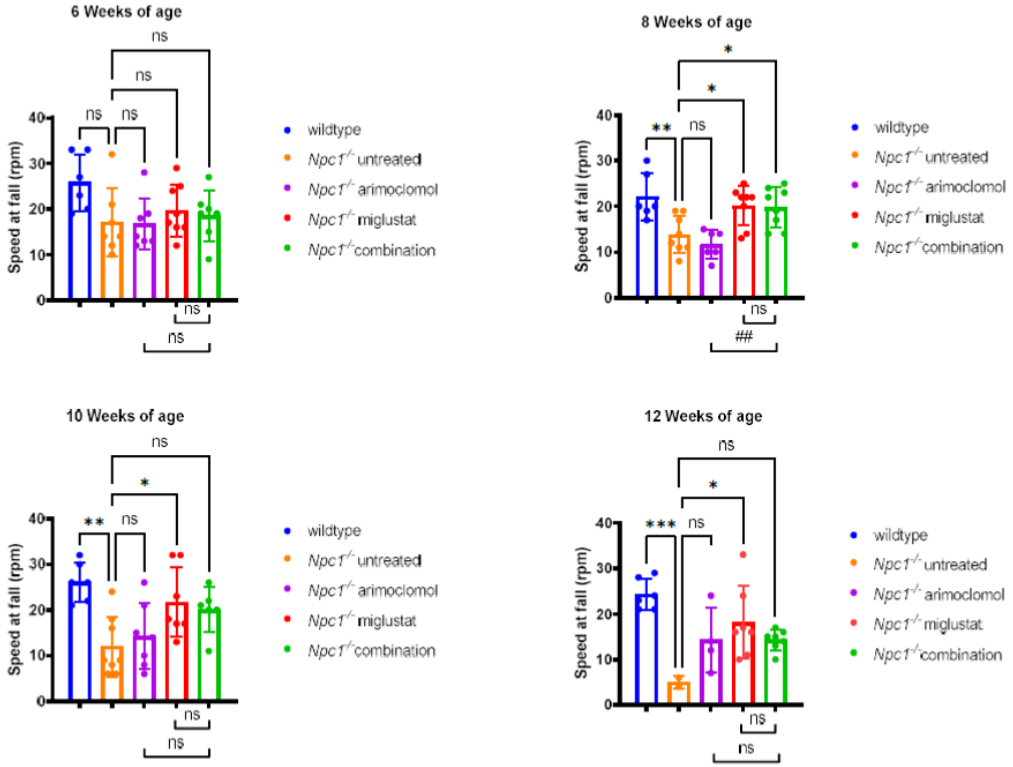


Observations

- Decrease for endpoint at all timepoints for KO vs WT
- No effect of arimoclomol alone relative to KO at any age
- Miglustat alone and miglustat+arimoclomol improved latency to fall at 8 weeks of age
- Trends for improved latency to fall for miglustat and miglustat+arimoclomol at several timepoints
- No differences between miglustat alone and miglustat+arimoclomol

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Figure 23. Effects of Therapies on Speed at Fall (Rotarod)



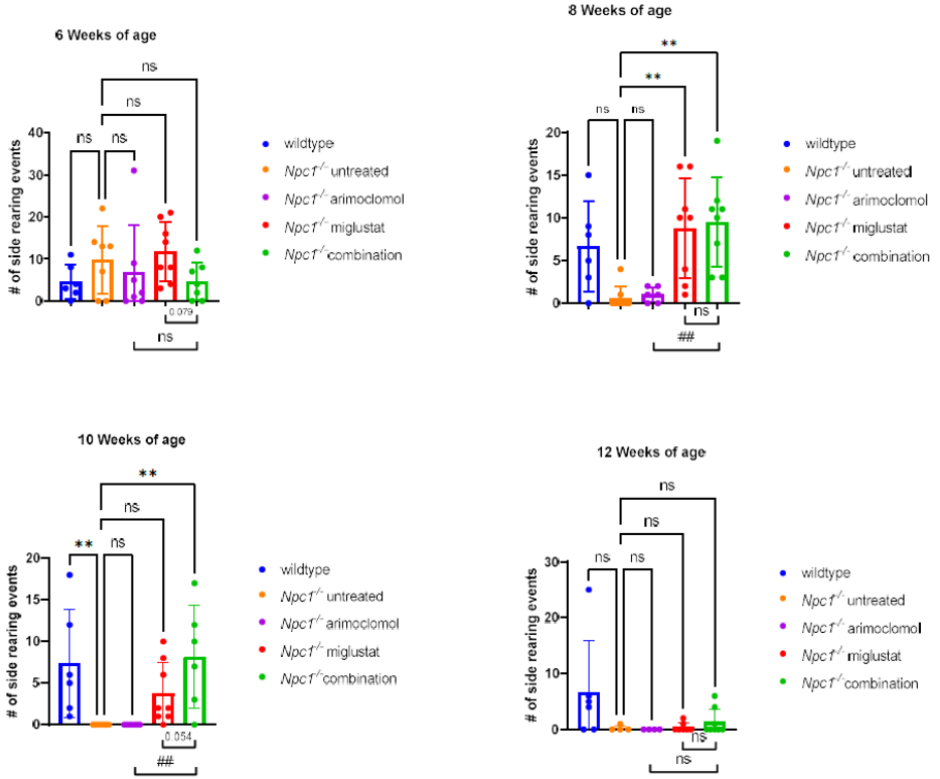
Observations

- Decrease for endpoint at all timepoints for KO vs WT
- No effect of arimoclomol alone relative to KO at any age
- Miglustat alone improved speed at fall at Weeks 8, 10, 12
- Miglustat+arimoclomol improved speed at fall at Week 10
- Trends for improved speed at fall for miglustat and miglustat+arimoclomol at several timepoints
- No differences between miglustat alone and miglustat+arimoclomol

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

The progressive inability of mice to rear on their hind legs, either unaided (center rearing) or when leaning against the cage wall (side rearing) is a measure of functional decline in Npc1$^{-/-}$ mice. Thus, motor function/coordination was measured by monitoring the rearing ability of mice in an open field test. Treatment with arimoclomol alone had no effect on side rearing, while miglustat alone and combination of arimoclomol and miglustat improved side rearing in a similar manner at Week 8. While it is apparent that combination of arimoclomol and miglustat improved side reading at Week 10 to a greater extent than miglustat monotherapy, there was no statistically significant difference between treatment with miglustat alone and combination of arimoclomol and miglustat (Figure 24).

Figure 24. Effects of Therapies on Side Rearing Activity



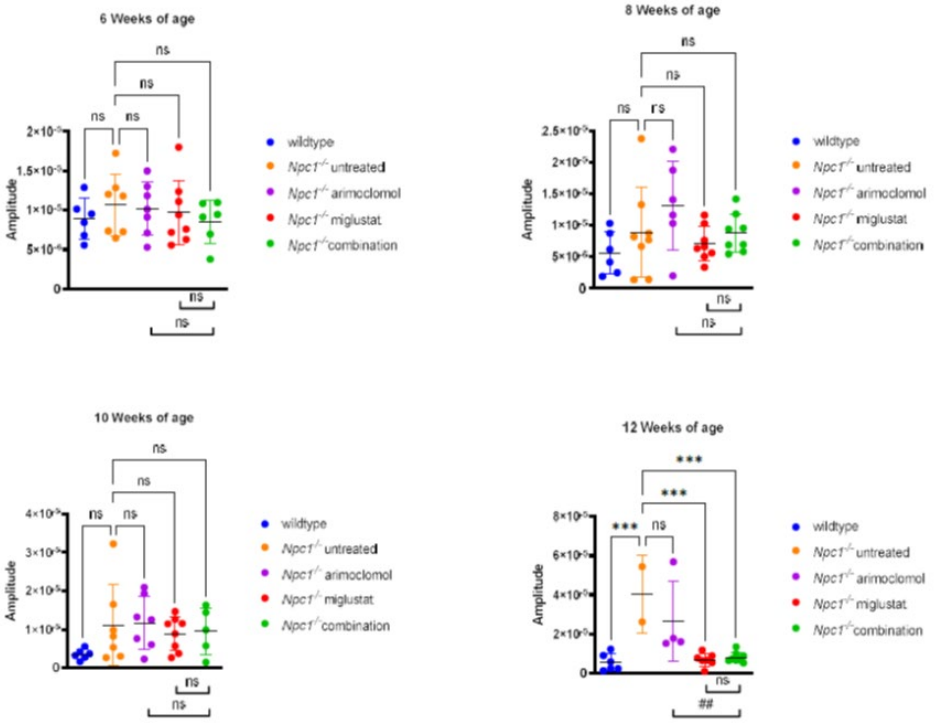
Observations

- No effect of arimoclomol alone relative to KO at any age
- Miglustat alone and miglustat+arimoclomol improved side rearing activity at Week 8 (no difference between miglustat and miglustat+arimoclomol)
- Miglustat+arimoclomol improved side rearing activity at Week 10
- No differences between miglustat alone and miglustat+arimoclomol at Weeks 8 and 12

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Neuronal degeneration is a corresponding feature of NPC pathogenesis in $Npc1^{-/-}$ mice. This is characterized by an age-dependent progressive loss of motor function and an increase in high frequency (32 to 55 Hz) tremor. Thus, evaluation of high frequency tremor, a pathological condition that is not generally present in healthy animals, was evaluated in this study. The untreated controls were not significantly different from WT animals until week 12. Arimoclomol alone did not reduce high frequency tremor despite a modest trend toward reduction at week 12 (not statistically significant); however, miglustat alone and the combination of arimoclomol and miglustat reduced high frequency tremors in a similar manner at week 12 (Figure 25).

Figure 25. Effects of Therapies on High-Frequency Tremor



Observations

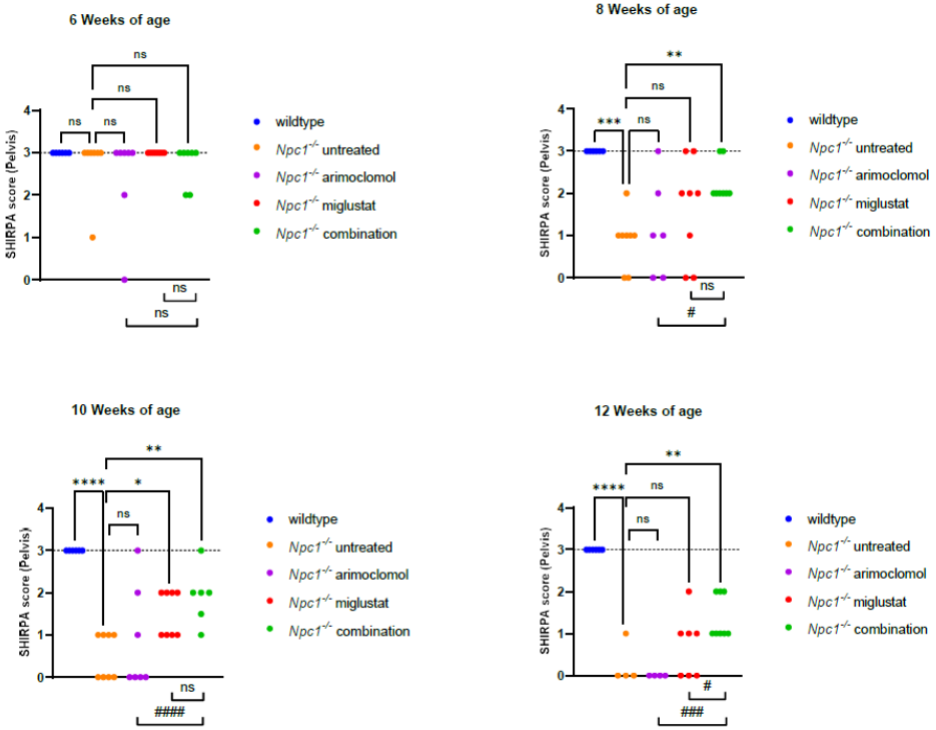
- Increased tremor at Week 12 in the KO vs WT
- No significant improvement with arimoclomol alone
- Miglustat alone and miglustat+arimoclomol improved amplitude at Week 12 (no difference between miglustat and miglustat+arimoclomol)

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

SmithKline Beecham, Harwell, Imperial College, Royal London Hospital, Phenotype Assessment (SHIRPA) is a standardized set of experimental procedures that are used to characterize the phenotype of genetically modified laboratory mice. SHIRPA procedures assessed behavioral symptoms like pelvis position, tail position, piloerection (coat appearance), respiratory rate (breathing), palpebral closure, and spontaneous movement, parameters which were previously shown to be affected in $Npc1^{-/-}$ mice.

In this battery, treatment with arimoclomol alone trended towards improvement in some SHIRPA parameters, but the effects were not statistically significant. Miglustat alone and the combination of arimoclomol and miglustat showed statistically significant improvements of NPC disease phenotypic parameters, including pelvic position (Figure 26), tail position (Figure 27), and piloerection (Figure 28) in $Npc1^{-/-}$ mice. The effects were not clearly consistent across the various SHIRPA parameters but the duration of the effect with the combination was often long and for one parameter (piloerection), the effect of the combination was statistically strong.

Figure 26. Effects of Therapies on Pelvic Elevation

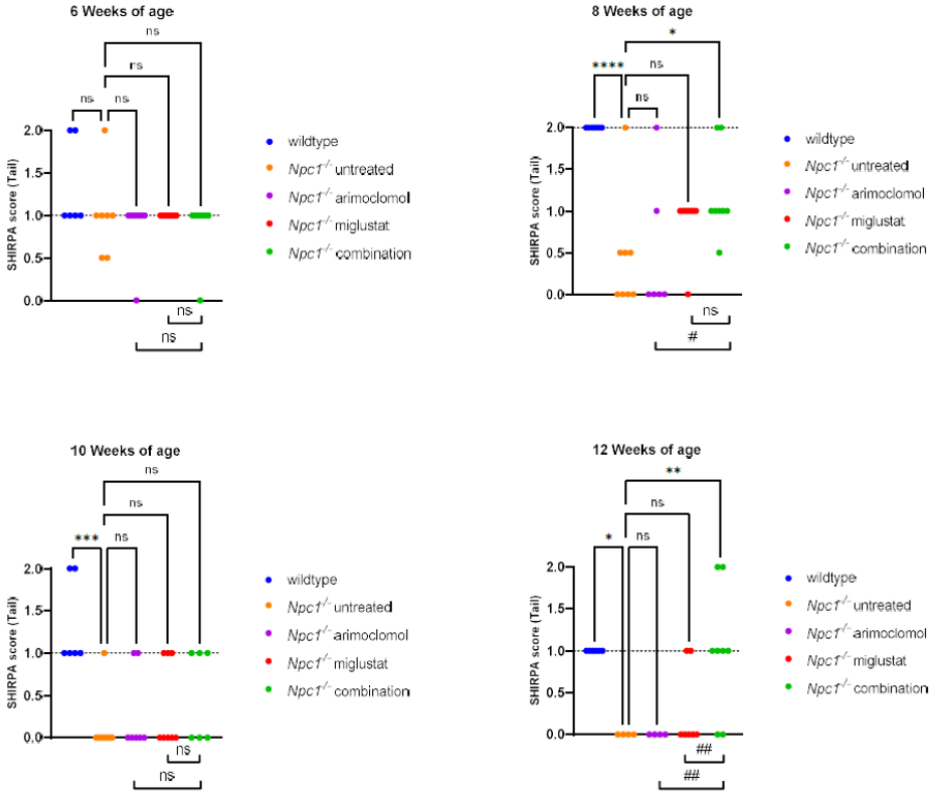


Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Observations

- Decreased score at Weeks 8, 10, 12 in the KO vs WT
- No significant improvement with arimoclomol alone
- Miglustat alone and Miglustat+arimoclomol improved pelvic elevation at Week 10 (no difference between miglustat and miglustat+arimoclomol)
- Miglustat+arimoclomol improved pelvic elevation at Weeks 8, 12

Figure 27. Effects of Therapies on Tail Elevation

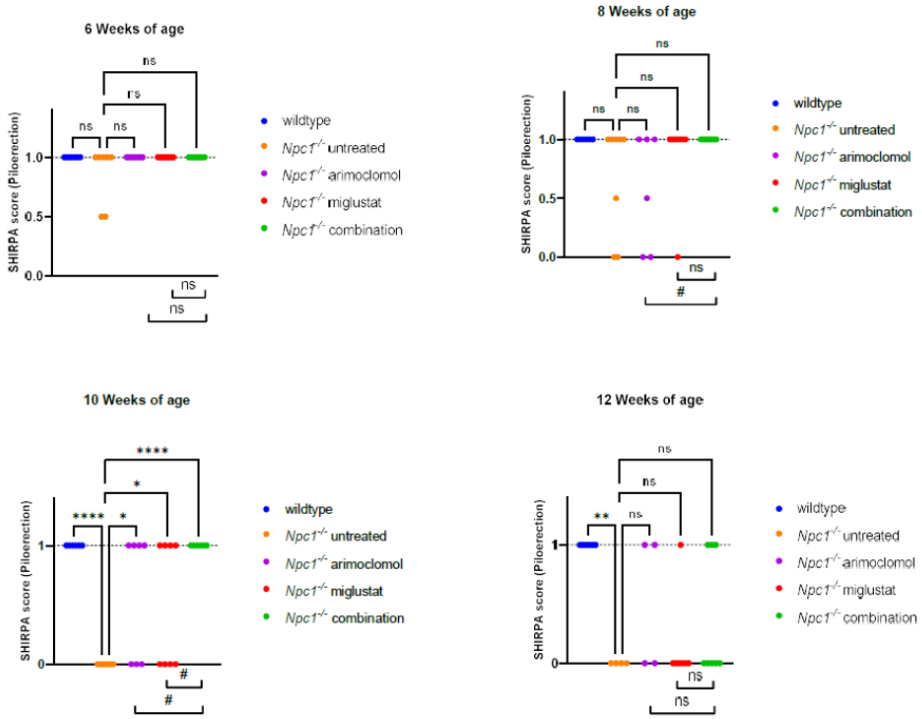


Observations

- Decreased score at Weeks 8, 10, 12 in the KO vs WT
- No significant improvement with arimoclomol alone
- Miglustat alone did not improve tail elevation
- Miglustat+arimoclomol improved tail elevation at Weeks 8 and 12

Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Figure 28. Effects of Therapies on Piloerection



Source: Excerpted from Applicant's Study Report CRO-1707310132-DOC-2110260043

Observations

- Decreased score at Weeks 10 and 12 in the KO vs WT
- Improved score at Week 10 for arimoclomol alone, miglustat alone, and miglustat+arimoclomol combination with combination greater response vs individual components

NPC1$^{-/-}$ Gait Analysis

Cerebellar ataxia is one of the major clinical signs in Npc1$^{-/-}$ mice and can be measured using rodent gait analysis, which was performed using the automated CatWalk system that measures a wide range of parameters related to rodent gait including stance, swing speed, step cycle, etc. A total of 63 gait parameters were assessed with this method. The reviewer prepared a summary table of statistically significant improvements in gait parameters after treatment with arimoclomol alone, miglustat alone, and combination of arimoclomol and miglustat. As shown in Table 16, arimoclomol alone had no effect on gait parameters, while miglustat alone and the combination of arimoclomol and miglustat improved several gait parameters in Npc1$^{-/-}$ mice at weeks 8 and 10.

Table 16. Effects of Therapies on Gait (CatWalk)

Drug	6 Weeks	8 Weeks	10 Weeks
Arimoclomol	0/63	0/63	1/63
Miglustat	1/63	33/63	41/63
Arimoclomol + Miglustat combination	0/63	23/63	23/63

Source: Reviewer; prepared with Applicant's data from Applicant's Study Report CRO-1707310132-DOC-2110260043

In conclusion, in the NPC1$^{-/-}$ mouse model and the NPC1$^{nmf/nmf}$ mouse model

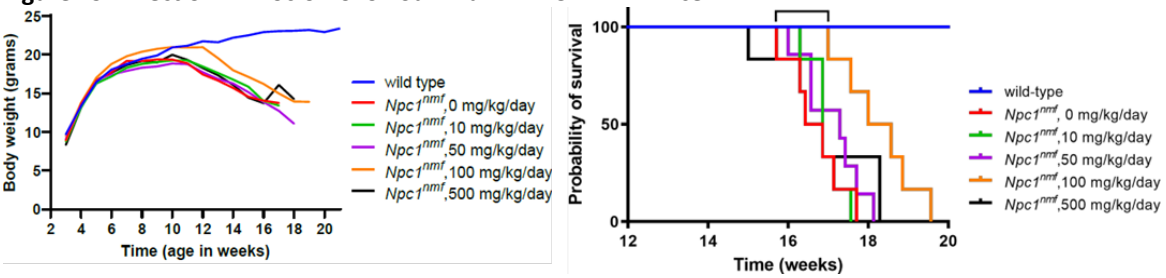
- There was an apparent effect of miglustat on survival.
- The effect of miglustat appeared to be enhanced by treatment with arimoclomol, despite the apparent absence of effect of arimoclomol alone on survival.
- There was a strong effect of miglustat and miglustat plus arimoclomol on the onset of high frequency tremor, which is considered a disease-related process.
  - There were minor effects of miglustat or miglustat plus arimoclomol on various aspects of gait and motor function; however, the effects were small in magnitude and of uncertain relationship to treatment given the overall inconsistency of effect across the various measurements performed.
  - Interpretation of these data is limited by the lack of data on the delivered dose and lack of information about the resulting pharmacokinetic exposures in treated animals.

Data on the Effects of Arimoclomol in NPC1$^{nmf/nmf}$ Mice

The Applicant conducted two studies in NPC1$^{nmf/nmf}$ mice, Studies 45 and 48. The gene defect in this model results from a point mutation at codon 1005 (A to G substitution). The model produces relatively normal levels of Npc1 mRNA but reduced levels of NPC1 protein. The Applicant states that this model has attenuated disease progression relative to the NPC1$^{-/-}$ model.

In Study 45 (CRO-1707310132-DOC-2201170045), the Applicant evaluated presymptomatic treatment at 3 weeks of age at doses of 0, 10, 50, 100, and 500 mg/kg/day in drinking water. They evaluated survival, as well as effects on various gait, posture, and motor functions. As shown in Figure 29, a modest but statistically significant effect on survival was observed at one dose level (100 mg/kg/day) compared with the concurrent control, but no effects were seen at higher or lower doses. This effect on survival at the 100 mg/kg dose level appeared to correlate with improved body weight. No significant effects were observed on any other endpoint.

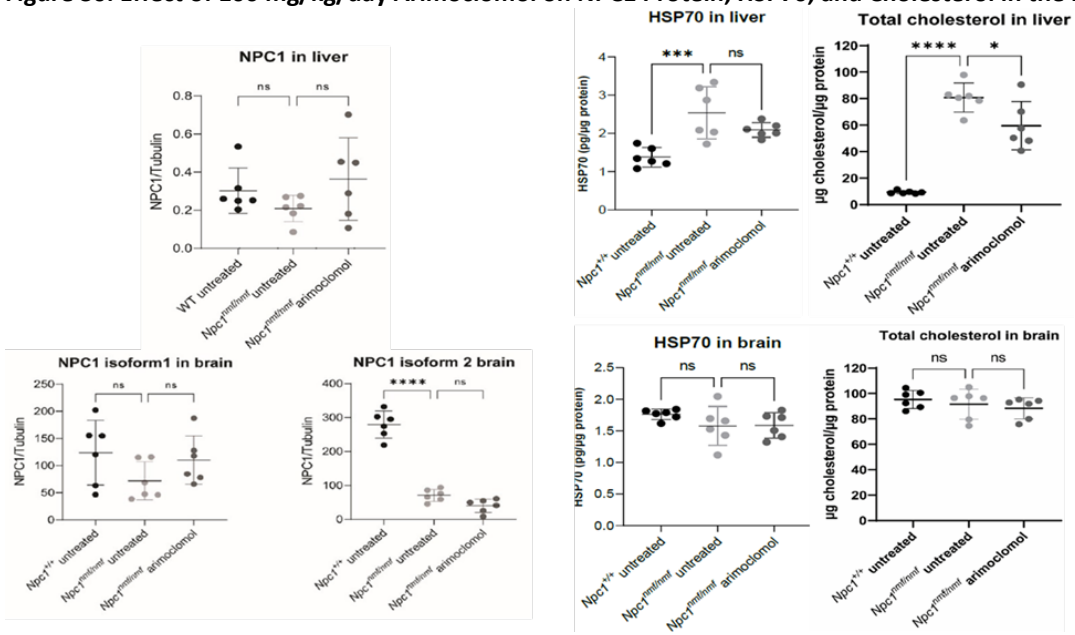
Figure 29. Effect of Arimoclomol on Survival in NPC1$^{nmf/nmf}$ Mice



Excerpted from the Applicant's submission – study report CRO-1707310132-DOC-2201170045

In Study 48 (CRO-1707310132-DOC-2203180048), the Applicant also evaluated the effects of arimoclomol in female mice treated with arimoclomol at a dose of 100 mg/kg/day. Mice were treated from 3 weeks of age and tissues were harvested for evaluation of NPC and HSP70 protein levels, and for evaluation of lipid levels at 12 weeks of age. Total cholesterol was reduced in the liver of NPC1$^{nmf/nmf}$ mice after arimoclomol treatment, but there was no effect on total brain cholesterol, and no effect on brain glycosphingolipid species (Figure 30).

Figure 30. Effect of 100 mg/kg/day Arimoclomol on NPC1 Protein, HSP70, and Cholesterol in the Livers and Brains of NPC1$^{nmf/nmf}$ Mice



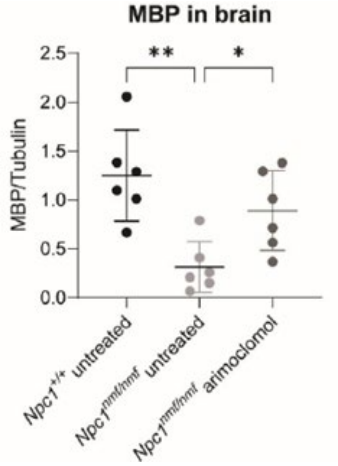
Observations

- In KO vs WT, increased cholesterol in liver, not brain; increased GSL levels in liver, not brain; reduced NPC1 isoform 2 in brain, not liver; and increased HSP70 in liver, not brain
- Arimoclomol reduced cholesterol in liver
- No arimoclomol effect on expression of brain NPC1 or HSP70

Source: Excerpted from the Applicant's submission – study report CRO-1707310132-DOC-2203180048

There was also no effect on levels of HPS70, NPC1 in the liver or brain. There was, however, an increase in myelin basic protein in the brains of mice treated with arimoclomol (Figure 31). Whether this was the result of reduced neurodegeneration and/or neuroinflammation in animals treated with arimoclomol cannot be established, as histopathology was not performed.

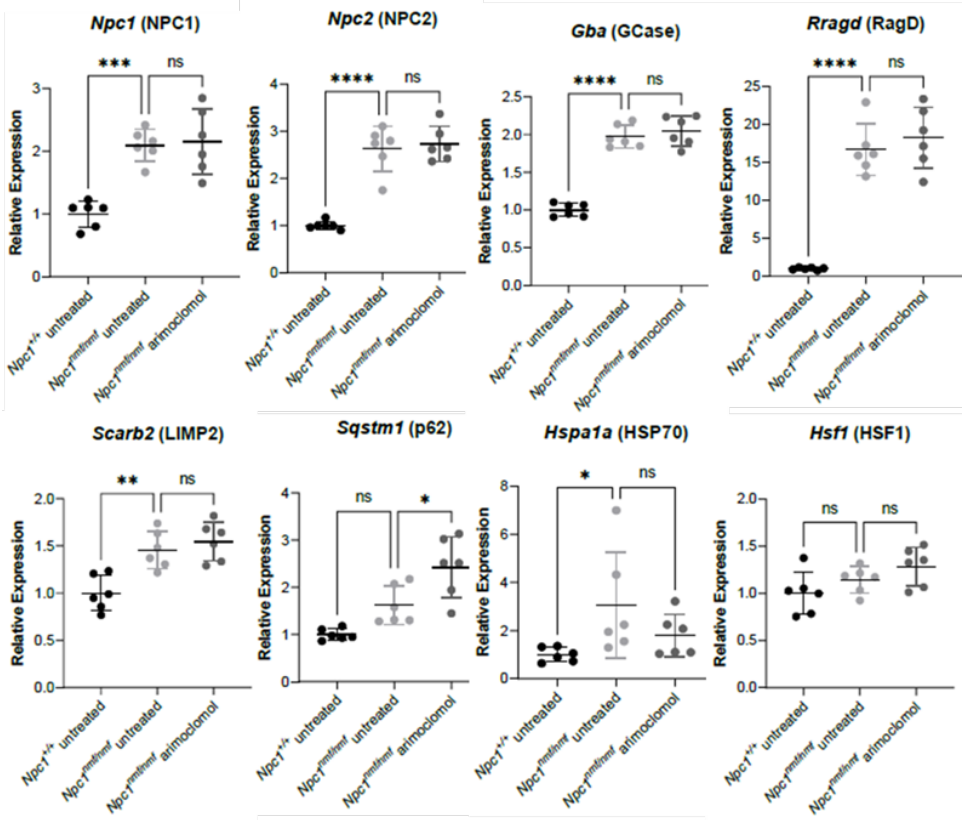
Figure 31. Effect of Arimoclomol on the Level of MBP in the Brain of NPC1$^{nmf/nmf}$ Mice



Excerpted from the Applicant's submission – study report CRO-1707310132-DOC-2203180048

There were also no effects in the livers of treated mice on any of the CLEAR network genes that were evaluated in cultured cells (Figure 32). Similarly, there were no effects on CLEAR network genes in the livers of treated mice (*BiP*, *ATF6*, *eIF2A*, *CHOP*, *p97*, *ApoE*, *ABCA1*; data not shown).

Figure 32. Effect of Arimoclomol on CLEAR Gene Expression in the Livers of NPC1$^{nmf/nmf}$ Mice Treated With 100 mg Arimoclomol for 9 Weeks



Source: Excerpted from the Applicant's submission – study report CRO-1707310132-DOC-2203180048

Overall, there was no apparent effect of genotype on the effect of arimoclomol in the NPC1$^{nmf/nmf}$ mouse model.

- A modest reduction in liver cholesterol was observed; however, the functional significance of this effect is unclear, as no effects were observed in the brains of treated animals. As the liver is expected to achieve higher concentrations than the brain following oral administration, this could suggest a potential to reduce cholesterol in the brain if higher exposures were achieved.
- Little to no effect was observed on expression of CLEAR network genes following treatment with arimoclomol at doses of 100 mg/kg/day.
- There was no effect of treatment on survival, despite initiation of treatment during the presymptomatic phase.
- Interpretation of these data is limited by the lack of data on the delivered dose and lack of information about the resulting pharmacokinetic exposures in treated animals, or information about the stability of the test article in drinking water.

Overall Summary and Assessment

Changes in CLEAR Gene Transcription

The Applicant's data show that arimoclomol induces nuclear translocation of the transcription factors, TFE3 and TFEB, which are involved in CLEAR gene expression. Because the effects described by the Applicant were predominantly observed at high concentrations and generally did not exhibit a dose-

response, there is concern that the effects were mediated by toxicity, rather than by a specific PD activity of the drug. Importantly, to assess the status of the cells at high arimoclomol exposures, no evaluation of markers of cellular viability and health in cells cultured with arimoclomol were performed. Because several toxicities can affect cellular metabolism leading to a reduction in mitochondrial ATP production (Eisner et al. 2018), it is important to determine the extent of cytotoxicity in cultures treated with high concentrations of arimoclomol. Because mitochondria coordinate the synthesis of several membrane phospholipids, it is also important to show that effects on mitochondrial function were not impairing lipid biosynthesis (Mesmin 2016).

Pharmacodynamic interactions between arimoclomol and miglustat appeared to have an additive effect compared to arimoclomol or miglustat alone. This was evident at gene level when arimoclomol increased the expression of CLEAR genes *NPC1*, *NPC2*, *GBA*, *GLA*, *RRAGD*, *SQSTM1*, and *HSPA1A* both in the absence of miglustat and in the presence of miglustat and the enhanced lysosomal gene expression and reduced filipin staining was observed at highest concentrations of both arimoclomol and miglustat. As noted above, studies of cell stress/viability were not performed so that cytotoxicity was not excluded as the mechanism of the altered gene expression very high drug concentrations (many-fold above clinical exposures).

Results in Genetically Altered NPC Animal Models: Survival, Mobility, and Tremor

The combination of arimoclomol and miglustat appeared to improve survival and mobility in $Npc1^{-/-}$ mice, relative to arimoclomol alone, suggesting, additivity of effect. Treatment with miglustat alone and combination of arimoclomol and miglustat also delayed body weight loss in $Npc1^{-/-}$ mice, while treatment with arimoclomol alone had no effect on body weight in this study. These effects were paralleled by effects of the combination on rotarod performance.

There was also no effect of arimoclomol alone on high-frequency tremor; however, treatment with miglustat or the combination of arimoclomol and miglustat significantly reduced high frequency tremors in the $NPC1^{-/-}$ mice. The effect of the combination, however, was not clearly different from that of miglustat alone.

Because the Applicant's research program focused largely on the effects of arimoclomol alone, the body of evidence to support a potential additive effect of miglustat is relatively small. The in vitro data with the combination are generally aligned with the effects observed in animals; there is an effect of miglustat on many of the parameters evaluated, and an apparent potential for additivity between arimoclomol and miglustat on some parameters (e.g., reduction in filipin staining; upregulation of some of the measured target genes). This information in combination with the observed effects of miglustat and the combination of miglustat and arimoclomol on survival in $NPC1^{-/-}$ mice suggest a potential for enhanced benefit with the combination.

Limitations of Animal Model Studies

The studies conducted with arimoclomol and/or miglustat, particularly those in animals, have significant drawbacks that limit their ability to inform the mechanism of these drugs in NPC. The lack of pharmacokinetic exposure data makes it nearly impossible to understand the effect of exposure on outcome in these studies, as the test article was administered in the feed (miglustat) and drinking water (arimoclomol). The arimoclomol concentrations used were well beyond those that were assessed for palatability. Because taste aversion leads to reduced consumption of water in rodents (Campbell et al. 2009), linearity of exposure cannot be assumed in these studies. Whether this masks a true effect of

arimoclomol in the treatment of mice with NPC is unclear, however, given the overall lack of evidence for its activity in vitro. Similarly, the data from in vitro studies are confounded by the high concentrations used and the inability to differentiate a treatment effect from the effects of toxicity.

Assessment

Overall, the data suggest that at very high concentrations, there may be an effect on TFE3 and TFEB which may lead to upregulation of NPC1; however, the concentrations studied were markedly higher than clinical exposure, and cell cytotoxicity related to such high drug concentrations was not excluded. Whether upregulation of NPC1 is beneficial would to some extent depend upon the ability of the chaperone apparatus that the Sponsor has invoked, to effectively deliver the protein to the intended location. It is also possible that in some or most cases, even if the protein were correctly localized, the mutant protein may not adequately reduce stored cholesterol from the lysosomal volume. The Applicant has not shown a significant benefit of NPC1 upregulation on cholesterol accumulation either in vitro or in vivo. For these reasons, it is impossible to determine by which mechanism(s), if any, arimoclomol acts to abrogate the underlying molecular defect in NPC.

3.1.3.4.2 Clinical Pharmacology Evidence

This section provides a summary of PD biomarker data and exposure-response analysis results for R4DNPCCSS in study NPC-002.

Evaluation of Pharmacodynamic Biomarkers

In the initial NDA submission, a total of eight biomarkers were explored in study NPC-002, including four PD biomarkers: heat shock protein (HSP) 70 in peripheral blood mononuclear cells (PBMCs), unesterified cholesterol in PBMCs, cholestane-triol (c-triol) in serum, and lysosphingomyelin-509 (lyso-SM-509) in plasma. HSP70 is intended to reflect the drug's proposed mechanism while unesterified cholesterol, c-triol, and lyso-SM-509 are nonspecific biomarkers reflecting different pathways of lipid metabolism.

In the NDA resubmission the Applicant included results of four PD biomarkers: c-triol, unesterified cholesterol, lyso-SM-509, and HSP70. The Applicant asserts that arimoclomol affects biochemical mechanisms such as the activation of transcriptional regulators, namely TFE3 and TFEB, which lead to downstream amplification of the cellular production of HSPs, specifically HSP70.

Unesterified Cholesterol

Unesterified cholesterol is related to NPC pathophysiology. Variants in *NPC1* or *NPC2* lead to impairments in intracellular trafficking and accumulation of unesterified cholesterol and, therefore, are the major accumulating lipids in patients with NPC. However, it is unclear how NPC1 and NPC2 cooperate to transport cholesterol within the brain and the precise mechanism underlying the manifestation of NPC is not fully understood.

Cholestane-triol

An excess of intracellular cholesterol along with enhanced oxidative stress in NPC promotes the formation of oxysterols, such as c-triol. C-triol concentrations are elevated in NPC patients, and assessment of c-triol concentrations is part of the diagnostic workup of NPC. However, the relationship between c-triol and unesterified cholesterol concentrations and severity of disease has not been established and it is unclear whether reductions in either biomarker have clinically meaningful impact.

Lyso-SM-509

Lyso-SM-509, more recently identified as N-palmitoyl-O-phosphocholine-serine, is a novel lipid utilized in a composite panel of biomarkers for screening and diagnosis of NPC. Elevation in plasma lyso-SM-509 concentrations in patients with NPC have been observed. Evidence thus far has not linked the elevation of lyso-SM-509 to disease severity or provided evidence that it may measure disease progression or a treatment response.

PD Biomarker Findings in NPC-002

In study NPC-002, the Applicant explored the effect of arimoclomol treatment on PD biomarkers from baseline of the double-blind phase to 12 months (data included in the initial NDA submission) and from baseline of the OLE phase to 48 months (data included in the NDA resubmission). In the double-blind phase of NPC-002, only Lyso-SM-509 demonstrated a significant treatment difference at 6 months; however, the data were inconsistent across the 6- and 12-month timepoints. None of the other PD biomarkers showed statistically significant differences between arimoclomol and placebo treatment groups at Months 6 or 12. The high variability in biomarker concentrations, low sample acquisition, and lack of consistent effect on the PD biomarkers make interpretation of any treatment related effect difficult.

In the OLE phase of NPC-002, there was a further lack of sample acquisition which led to PD biomarker assessment in up to 26 subjects on arimoclomol who continued arimoclomol treatment in the OLE (i.e., arimoclomol-arimoclomol group) and up to 15 patients who received placebo treatment in the double-blind phase and arimoclomol in the OLE (placebo-arimoclomol group). The PD biomarker data in the OLE phase showed inconsistent trends and high inter-subject variability with no statistical difference or improvement when compared to baseline values.

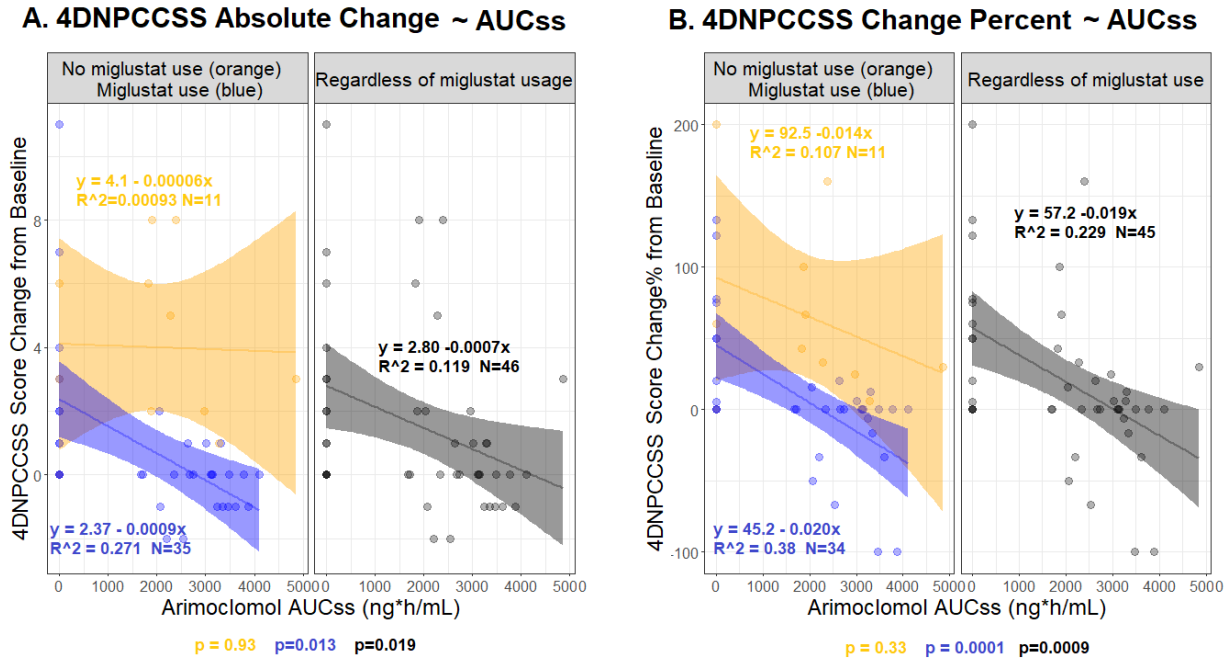
Overall, the PD biomarker data presented in the original NDA submission and the NDA resubmission have numerous limitations including missing data, low sample acquisition, and high inter-subject and intra-subject variability. Moreover, the role of these biomarkers in disease progression and their correlation with clinical presentation of NPC are not well-understood, and the systemic concentrations of these biomarkers may not reflect the biomarker concentrations in relevant target tissue (e.g., brain). 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 Relationship for Efficacy

We explored the exposure-response (E-R) relationship between arimoclomol area under the concentration-time curve at steady state and change of 4DNPCCSS, as absolute change (Figure 33A) or percent change (Figure 33B) from baseline to Month 12 in NPC-002. Given the limited number of subjects, the univariate E-R analysis is considered exploratory and is for trend illustration. The analysis, which included placebo-treated patients with no exposure to arimoclomol, showed patients with higher arimoclomol exposure had a greater decrease in 4DNPCCSS%. There was numerically less reduction in 4DNPCCSS in patients who received arimoclomol alone compared to those who received arimoclomol with concomitant use of miglustat (the orange dots versus blue dots). The 4DNPCCSS differences at baseline may indicate differences in the severity of disease in patients. Given the differences at the baseline between the subgroups with and without concomitant miglustat and differences between percent change and absolute change, the degree of change may be confounded by the baseline values. Overall, the interpretation of the E-R analysis results is limited by the small sample size, the majority of

patients were receiving concomitant miglustat, and other potential confounding factors such as differences in disease severity at baseline among subgroups.

Figure 33. Exposure-Response Relationships Between the AUC of Arimoclomol at Steady State (AUCss) and Percentage or Absolute Change of 4DNPCCSS in NPC-002



Source: FDA reviewer's analysis results using data in adep.xpt.
Note that three patients with missing PK data were not included in the analysis.

3.1.3.4.3 Clinical Evidence

The Applicant provided clinical data and analyses from (1) the open label-extension of study NPC-002 (NPC-002 OLE), (2) the observational study NPC-001, (3) natural history data from the ongoing NIH natural history study of NPC, and (4) patients with NPC treated with arimoclomol under expanded access protocols. The medical literature was also used to support the Agency's review and interpretation of the clinical data.

NPC-002 Open-Label Extension

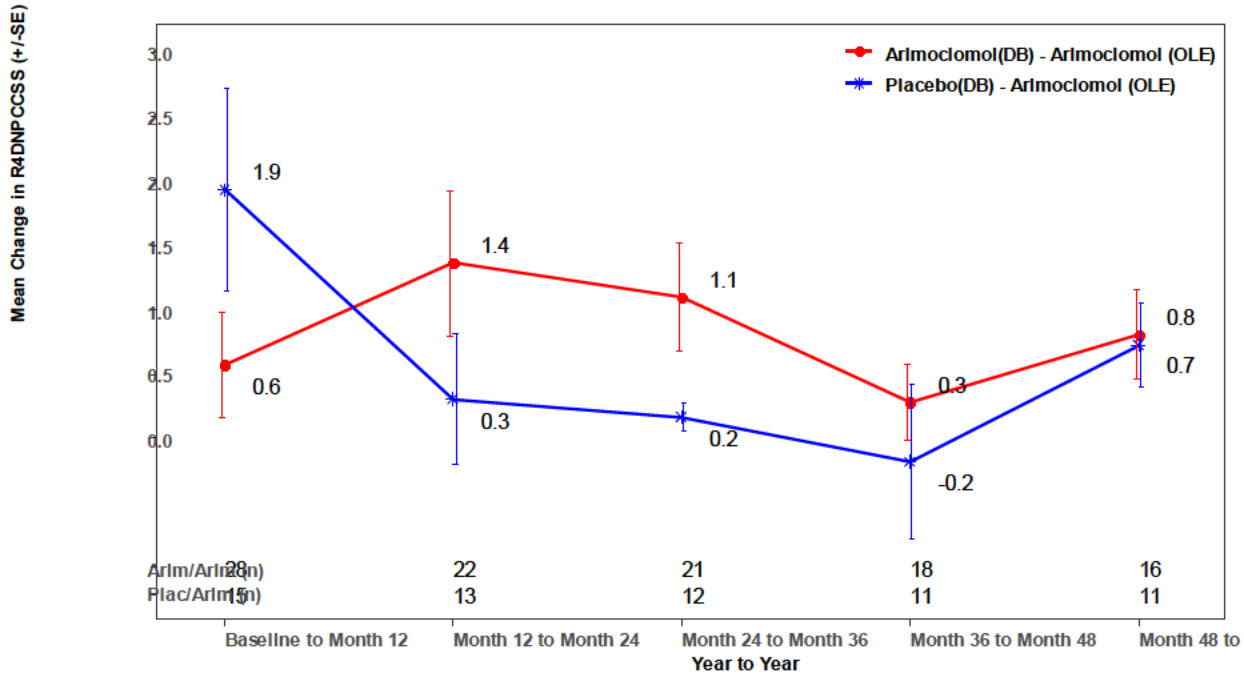
Eligible subjects from study NPC-002 had the option to continue into an open-label extension study (NPC-002 OLE) for up to 48 additional months of arimoclomol. Forty-one subjects from study NPC-002 continued into NPC-002 OLE, with 27 subjects completing all 48 months (for a total of 60 months of treatment for those initially randomized to arimoclomol during the double-blind phase of NPC-002). Thirty-three subjects (33/41, 80.5%) in the OLE had been taking concomitant miglustat as part of their baseline care regimen when they enrolled in NPC-002.

Figure 34 presents year-to-year change in R4DNPCCSS for both the DB phase and OLE phase. Subjects randomized to placebo in study NPC-002 (n=15) had a mean change in R4DNPCCSS from baseline of 1.9 points at 12 months. The mean change from 12 months to 24 months in R4DNPCCSS decreased to 0.3 after starting treatment with arimoclomol during the first year of the OLE. For each additional year on open-label treatment with arimoclomol, the year-to-year mean change in R4DNPCCSS scores for subjects who started study NPC-002 on placebo and then started treatment with arimoclomol in the OLE

continued to be numerically smaller (potentially indicating slower disease progression) than during the double-blind phase of study NPC-002. However, the interpretation of these observations is limited given the lack of an adequate control for this group and unblinded assessments of the R4DNPCCSS during the OLE.

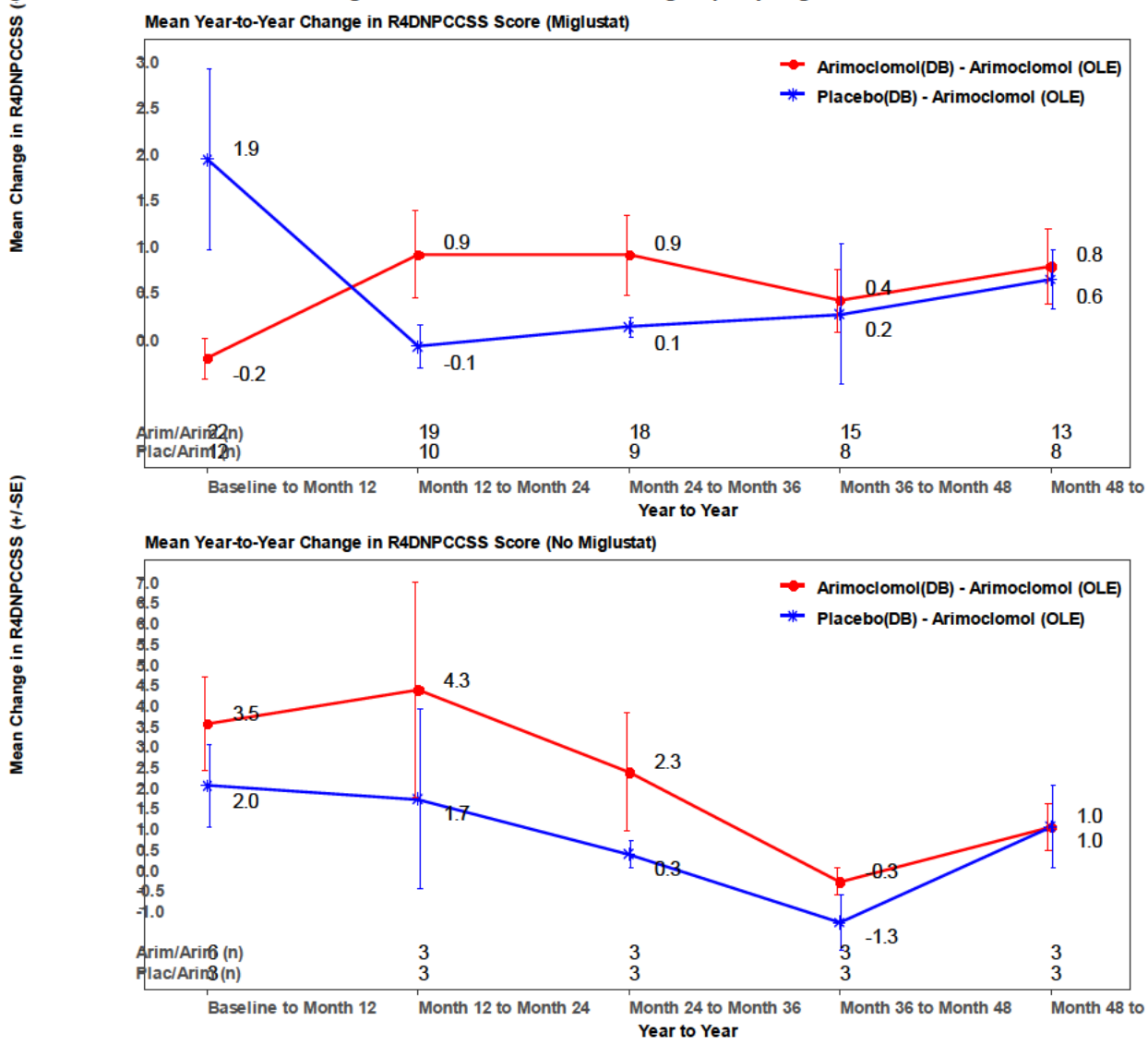
Subjects randomized to arimoclomol in study NPC-002 had a mean change in R4DNPCSS from baseline of 0.6 points at 12 months. The mean change in R4DNPCCSS scores for each year on continued treatment on arimoclomol in the OLE for the subjects initially randomized to arimoclomol in study NPC-002 (n=28) were more variable and demonstrated an initial apparent worsening in the mean change in R4DNPCCSS of 1.4 for the first year of OLE treatment (from 12 months to 24 months). The mean year-to year change in R4DNPCCSS for the following three years of treatment in this group was 1.1, 0.3, and 0.8, respectively. To investigate the period of apparent worsening during the first year of the OLE, the year-to-year mean change in R4DNPCCSS in subjects taking arimoclomol in addition to concomitant miglustat during the OLE were compared to subjects who were not taking miglustat (Figure 35). Subjects in the OLE who were taking miglustat as part of their standard care regimen in addition to arimoclomol (n=22) had a mean change in R4DNPCCSS of 0.9 at the end of the first year in the OLE (a smaller numeric increase than the total cohort initially randomized to arimoclomol). Subjects in the OLE who were initially randomized to arimoclomol and were not also taking miglustat had a mean change in R4DNPCCSS of 4.3 during the same time period. The increase in disease progression during the first year of the OLE appears to be driven in part by the few subjects who were not also on miglustat and had rapid disease progression.

Figure 34. Mean Year-to-Year Change in R4DNPCCSS Score in Study NPC-002 OLE



Source: FDA's figure.
The row 'Arim/Arim (n)' presents the number of patients who were treated with arimoclomol for both double-blind phase and OLE. The row 'Plac/Arim (n)' presents the number of patients who were treated with placebo for double-blind phase and then switched to arimoclomol for OLE after 12 months.
Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SE, standard error

Figure 35. Mean Year-to-Year Change in R4DNPCCSS Score for Subgroups by Miglustat Use



Source: FDA's figure.
The row 'Arim/Arim (n)' presents the number of patients who were treated with arimoclomol for both double-blind phase and OLE. The row 'Plac/Arim (n)' presents the number of patients who were treated with placebo for double-blind phase and then switched to arimoclomol for OLE after 12 months.
Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SE, standard error

Study NPC-001

Study NPC-001 was a prospective noninterventional study that enrolled 36 subjects 2 to 19 years of age with NPC to assess their clinical course over time using the same primary endpoint as for study NPC-002. Subjects who enrolled in study NPC-001 were assessed at two time points, (1) baseline visit and (2) end of study visit, that occurred between 6 and 14 months after the baseline assessment. The mean change from baseline to the end of study visit in R4DNPCCSS was 1.4 for the total cohort (all enrolled subjects in NPC-001). A total of 27 subjects in NPC-001 subsequently enrolled in NPC-002. Out of those 27 subjects, 18 subjects were subsequently randomized to arimoclomol in NPC-002. The mean change from baseline to the end of NPC-001 in R4DNPCCSS for these subjects was 1.6; while the mean change in R4DNPCCSS from baseline at the end of study NPC-002 after treatment with arimoclomol was 0.78, demonstrating

an apparent slowing of disease progression. This analysis is limited because the subjects are serving as their own historical control and the mean change during study NPC-001 is not a direct comparison of year-to-year change due to the varied duration of observation (6 to 14 months). Therefore, definitive conclusions regarding a treatment effect cannot be drawn from the data in this comparison.

Table 17. Summary of R4DNPCCSS Score in Study NPC-001 (Subset of Subjects Enrolled in NPC-002)

	Randomized Group in NPC-002		
	Arimoclomol	Placebo	Total
Variable	**N=18**	**N=9**	**N=27**
Baseline of NPC-001			
Mean (SD)	6.72 (5.07)	6.33 (5.66)	6.59 (5.17)
Median (min, max)	5.5 (0.0, 17.0)	4.0 (0.0, 19.0)	5.0 (0.0, 19.0)
End of NPC-001			
Mean (SD)	8.33 (5.59)	7.67 (5.59)	8.11 (5.49)
Median (min, max)	7.5 (1.0, 20.0)	6.0 (0.0, 19.0)	6.0 (0.0, 20.0)
Change from baseline to end			
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)

Source: FDA's table.
Abbreviations: max, maximum; min, minimum; N, number of subjects; R4DNPCCSS, re-scored 4-Domain Niemann-Pick disease type C Clinical Severity Scale; SD, standard deviation

NPC-002 OLE Compared to Natural History

Per the FDA's request, the Applicant provided a post hoc comparison of the NPC-002 OLE data to annual assessments for 48 months from subjects in a natural history study of NPC conducted at the NIH. In the Applicant's analyses, both the NPC-002 OLE arimoclomol arm and the NIH arm were restricted to patients with at least 4 years of follow-up, which resulted in 32 arimoclomol and 23 NIH patients in the database. Given the limited number of subjects in both arms, traditional direct case matching for external comparison appeared to be infeasible. Alternatively, the Applicant used two approaches to adjust for confounding factors. The first approach used a propensity score inverse probability of treatment weighting. In principle, this approach aims to mitigate the impact of imbalance in baseline covariates between the two arms by assigning different weights to subjects depending on their baseline covariates. Specifically, the weights are calculated via a logistic regression model as study arm (1 for NPC-002 OLE or 0 for NIH arm) being a binary response variable. The Applicant implemented three different logistic regression models by varying the set of covariates: (1) sex, miglustat use, baseline score, and baseline age, (2) sex, miglustat use, baseline score, and age at first neurological symptom, and (3) sex, miglustat use, baseline score, baseline age, and age at first neurological symptom (see the footnote of Table 18). The second approach attempted to match cases by sex, age of onset of neurological symptoms, baseline 4DNPCCSS score and miglustat use. Subjects were categorized into strata by all 4 of these variables. Any strata that did not have at least one patient in each arm was removed from the analysis. The demographics of the NPC-002 OLE subjects compared to NIH natural history subjects that resulted from both approaches are detailed in Table 18.

Table 18. Demographics Using IPTW and Case Matching

	IPTW								Case Matching	
	Before Weighting		Weighted [1]		Weighted [2]		Weighted [3]			
Timepoint Statistics	Ari. (N=32)	NIH (N=23)	Ari. (N=32)	NIH (N=23)	Ari. (N=32)	NIH (N=23)	Ari. (N=32)	NIH (N=23)	Ari. (N=28)	NIH (N=17)
Baseline 4DNPCCSS Score										
Mean	8.78	2.87	6.43	3.55	6.32	3.55	6.43	3.57	8.46	3.53
(SD)	(6.205)	(2.599)	(5.944)	(2.317)	(6.003)	(2.308)	(5.949)	(2.321)	(6.149)	(2.577)
Median	7.50	3.00	4.00	4.00	4.00	4.00	4.00	4.00	7.50	4.00
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Max	20.0	7.0	20.0	7.0	20.0	7.0	20.0	7.0	20.0	7.0
Sex										
Female (Percent)	(50.0)	(43.5)	(48.5)	(43.7)	(48.6)	(44.1)	(48.0)	(43.3)	(46.4)	(47.1)
Male (Percent)	(50.0)	(56.5)	(51.5)	(56.3)	(51.4)	(55.9)	(52.0)	(56.7)	(53.6)	(52.9)
Miglustat Use										
No (Percent)	(18.8)	(21.7)	(15.8)	(21.9)	(15.6)	(21.7)	(16.0)	(22.7)	(10.7)	(17.6)
Yes (Percent)	(81.3)	(78.3)	(84.2)	(78.1)	(84.4)	(78.3)	(84.0)	(77.3)	(89.3)	(82.4)
Baseline Age										
Mean	13.05	9.54	12.11	11.12	12.12	11.10	12.15	11.14	12.94	11.75
(SD)	(5.028)	(8.737)	(5.162)	(7.719)	(5.247)	(7.652)	(5.139)	(7.695)	(4.816)	(8.888)
Median	12.95	7.67	12.50	11.75	12.50	11.75	12.50	11.75	12.66	12.17
Min	3.2	0.3	3.2	0.3	3.2	0.3	3.2	0.3	4.4	0.7
Max	20.4	35.8	20.4	35.8	20.4	35.8	20.4	35.8	20.4	35.8
Age of Neurological Symptom Onset										
Mean	5.04	5.03	5.16	5.49	5.22	5.44	5.25	5.41	4.76	5.69
(SD)	(3.788)	(4.351)	(4.008)	(3.973)	(4.057)	(3.940)	(4.020)	(3.964)	(3.623)	(4.805)
Median	4.00	3.00	4.00	3.00	4.00	3.00	4.00	3.00	4.00	5.00
Min	0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0
Max	12.3	18.0	12.3	18.0	12.3	18.0	12.3	18.0	12.0	18.0

Source: Applicant's table.
[1] Weighted on sex, miglustat use, baseline age, baseline 4DNPCCSS score.
[2] Weighted on sex, miglustat use, age of onset of neurologic symptoms, baseline 4DNPCCSS score.
[3] Weighted on sex, miglustat use, baseline age, age of onset of neurological symptoms, baseline 4DNPCCSS score.

The subjects were well matched using either approach for sex, age of onset of neurological symptoms and miglustat use. There was an imbalance in baseline 4DNPCCSS scores between the NPC-002 OLE cohort and the NIH cohort using either approach, with the NIH cohort being more mildly affected at baseline with lower mean scores.

A comparison of 4DNPCCSS scores from baseline to 48 months demonstrated a mean difference of –0.4 points (p=0.688-0.744) for any of the inverse probability of treatment weighting methods (Table 19). The comparison of 4DNPCCSS scores using the alternative case matching by strata method demonstrated a mean difference at 48 months of –0.9 (p=0.411). The analyses numerically favored the arimoclomol arm but neither approach provided nominal p-values <0.05. This analysis had several notable limitations. The subjects from the NIH cohort who met the Applicant's criteria for inclusion in the analysis had wide variability in assessment timepoints due to the non-interventional nature of the study and a requirement for travel to the NIH for assessments. In addition, there is a potential that administration and scoring of NPCCSS may differ between the two cohorts.

Another important limitation is that NIH subjects who had initiated other investigational therapies were not excluded from the analysis. In addition to 7 subjects who initiated miglustat treatment after the baseline assessment, there were 9 who initiated 2-hydroxypropyl-β-cyclodextrin (and one subject who initiated both). The largest number of additional treatment initiations occurred between the 12 and 24 months visit timepoints. Lastly, while this does not necessarily impact a comparison between scores at 48 months, it should be noted that 4DNPCCSS without re-scoring of the swallowing domain were used by the Applicant for these analyses because re-scored values were not available for the NIH cohort.

Table 19. Estimated Mean (SE) Change From Baseline to Month 48 in 4DNPCCSS (NPC-002 OLE vs. NIH NHS)

Method	Arimoclomol (NPC-002 OLE)	Placebo (NIH NHS)	Difference (95% CI)	p-value
IPTW 1[1]	2.3 (0.63)	2.7 (0.89)	-0.4 (-2.6, 1.8)	0.744
IPTW 2[2]	2.3 (0.62)	2.7 (0.89)	-0.4 (-2.5, 1.8)	0.736
IPTW 3[3]	2.3 (0.63)	2.7 (0.89)	-0.4 (-2.6, 1.8)	0.688
Case matching[4]	1.7 (0.64)	2.6 (0.84)	-0.9 (-3.1, 1.3)	0.411

Source: FDA's table summarizing the Applicant's tables.

[1] Weighted on sex, miglustat use, baseline age, baseline 4DNPCCSS score.

[2] Weighted on sex, miglustat use, age of onset of neurologic symptoms, baseline 4DNPCCSS score.

[3] Weighted on sex, miglustat use, baseline age, age of onset of neurological symptoms, baseline 4DNPCCSS score.

[4] Subjects were categorized into strata by sex, age of onset of neurological symptoms (0-2 years, 3-12 years, 13-16 years, 17-21 years, ≥22 years), baseline 4DNPCCSS score (0-4, 5-9, ≥10), and miglustat use. Any strata that did not have at least one patient in each arm was removed from the analysis.

The estimated mean (SE) changes were obtained from ANCOVA including treatment and baseline 4DNPCCSS score.

Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale, SE, standard error, OLE, open-label extension phase, NHS, natural history study, IPTW, inverse probability of treatment weighting

Arimoclomol Expanded-Access Programs

The Applicant submitted data from 81 patients who received arimoclomol through expanded access in the U.S., only 12 of whom had completed both their 1- and 2- year visits within a +/- 6- week window of their planned study visits. Several notable limitations with these data, in addition to the small patient numbers, are the lack of an adequate control for comparison, baseline heterogeneity across treated patients, the lack of standardization of assessment time points and NPCCSS administration at each clinical site, and biases associated with open-label drug administration. Therefore, conclusions regarding potential efficacy are not possible and the review team did not consider these data adequate to be supportive of a drug effect.

Summary of Additional Clinical Evidence

The additional clinical evidence submitted by the Applicant appears to show a slowing of disease progression after initiation of arimoclomol in subjects randomized to placebo in NPC-002 and in subjects in study NPC-001 who enrolled in NPC-002 and were randomized to arimoclomol. NPC-002 OLE appears to demonstrate continued relatively slow progression of disease. However, given the lack of a control group in NPC-002 OLE and the other limitations to the additional clinical evidence discussed above, definitive conclusions regarding a treatment benefit of arimoclomol cannot be drawn from these data. A period of apparent disease worsening for subjects initially randomized to arimoclomol between 12 to 24 months after randomization appears to have been driven by patients not on miglustat with severe disease trajectories. Year-over-year mean change in NPC disease severity is less variable in subjects on concomitant miglustat.

Post hoc comparison to an external natural history cohort did not reach statistical significance and was limited by small numbers, baseline imbalances and the use of investigational products in addition to arimoclomol in the comparison cohort.

We ask the Advisory Committee to consider whether the additional clinical evidence submitted by the Applicant supports the efficacy results of the pivotal trial.

3.1.3.4.4 Overall Assessment of Nonclinical, Clinical Pharmacology and Additional Clinical Data and Their Adequacy to Together Serve as Confirmatory Evidence

Multiple lines of evidence (nonclinical, clinical pharmacology and clinical, all discussed above) were submitted by the Applicant to provide confirmatory evidence of the treatment effect of arimoclomol observed in Trial NPC-002. Given the limitations of the clinical pharmacology evidence (detailed in

Section 3.1.3.4.2), the review team is unable to draw conclusions regarding a treatment effect of arimoclomol from this line of evidence. While the nonclinical evidence provides support for the apparent treatment effects of arimoclomol and miglustat observed in Study NPC-002, there are uncertainties and limitations with the nonclinical data, as detailed in Section 3.1.3.4.1. Additionally, the clinical data appears to show a slowing of disease progression after initiation of arimoclomol in subjects randomized to placebo in NPC-002 and in subjects in study NPC-001 who enrolled in NPC-002 and were randomized to arimoclomol. NPC-002 OLE also appears to demonstrate continued relatively slow progression of disease. However, this additional clinical evidence also has limitations, as discussed in Section 3.1.3.4.3. The review team does not consider that either the nonclinical evidence or the additional clinical evidence *alone* provides adequate confirmatory evidence. However, the review team asks the Advisory Committee to consider whether these lines of evidence, *taken together*, may provide adequate confirmatory evidence of the treatment effect observed in the single adequate and well-controlled trial.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

The first review cycle for this NDA application conducted between July of 2020 and June of 2021 encompassed safety data from 50 subjects from trial NPC-002 for dosages of 93-372 mg/day divided three times daily and placebo. Preliminary data from the open label extension (OLE) of NPC-002 for up to 12 months duration as well as data from placebo-controlled studies of arimoclomol in other indications (amyotrophic lateral sclerosis, inclusion body myositis, and GD) were also reviewed for safety signals and subject withdrawals or deaths.

Safety results received to date from the NPC-002 OLE and trials for other indications were not pooled with trial NPC-002. When the original NDA submission was reviewed in 2020-2021, arimoclomol was found to be relatively safe for use in the proposed to-be marketed dosages. The most common adverse reactions with arimoclomol identified in NPC-002 occurring at least 5% more commonly in the treatment arm than comparator arm were weight loss, decreased appetite, upper respiratory tract infections and urticaria. Hypersensitivity reactions (including urticaria and angioedema) and serum creatinine elevation were also reported, both of which were reversible with arimoclomol discontinuation.

Miglustat is used off-label in the majority of U.S. patients with NPC. In study NPC-002, 78% of subjects were taking miglustat at the time of enrollment. Miglustat is approved for NPC in several non-US countries and approved for adults with GD in the United States. The current labeling for miglustat contains Warnings and Precautions for the following: tremor, gastrointestinal (GI) events such as diarrhea and weight loss, peripheral neuropathy, and thrombocytopenia. Similar findings, particularly related to the GI events of weight loss, diarrhea, and vomiting, were identified in study NPC-002 in both the arimoclomol and placebo arms, making interpretations of AEs strictly related to arimoclomol more challenging.

In the current resubmission, with the addition of up to 48 months of additional exposure data from OLE from study NPC-002 and additional data from arimoclomol in other indications as listed in Table 20, the safety profile of arimoclomol has not changed. The adverse events identified during the previous review cycle remained the focus of the safety review in this cycle.

Table 20. Data Submitted to Support the Safety of Arimoclomol

Study Type	Trial	Blinding	Trial Duration	Treatment Exposure (mg Base Strength)	Number of Subjects
NPC					
Phase 3	NPC-002	Double-blinded	12 months	93-372 mg/day divided tid, 54 weeks	50
OLE for NPC-002	NPC-002 OL	Open label extension	48 months	93-372 mg/day divided tid, up to 48 months	41
Other indications (IBM, ALS, GD)					
Phase 2/3 study in patients with IBM	IBM4809	Double-blinded	21 months	248 mg divided tid	151
OLE from IBM4809	IBM-OLE	Open label extension	42 months	248 divided mg tid	121
Phase 2/3	ORARIGAU-01	Double-blinded	6 months	186-744 mg/day divided tid	39
OLE from ORARIGAU-01	ORARIGAU-01 OL	Open label extension	ongoing	186-744 mg/day divided tid	34
Phase 3 study in patients with ALS	ORARIALS-01	Double-blinded	18 months	248 divided mg	245
OLE from ORARIALS-01	ORARIALS-02	Open label extension	36 months	248 divided mg	120

Source: FDA's table summarizing the Applicant's tables.
Abbreviations: NPC, Niemann-Pick disease type C; OLE, open-label extension phase; IBM, inclusion body myositis; GAU, Gaucher disease; ALS, amyotrophic lateral sclerosis

3.2.2 Safety Summary

Gastrointestinal adverse events (diarrhea, constipation) were the most commonly observed non-infectious adverse events in Study NPC-002. Metabolism and nutrition related adverse events (decreased weight and appetite) were the second most common, and both categories are also currently reported in the FDA[2] and European Medicines Agency labeling for miglustat (EMA 2020; FDA 2020). Gastrointestinal events were also common in the placebo arm in study NPC-002; Table 21 lists the most common adverse reactions that occurred 5% more often in the arimoclomol treatment arm than in the placebo arm.

[2] See miglustat at https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwj4k6CgzIOHAxWxGlkFHaYACgQQFnoECBYQAQ&url=https%3A%2F%2Fwww.accessdata.fda.gov%2Fdrugsatfda_docs%2Flabel%2F2020%2F021348s016lbl.pdf&usg=AOvVaw2OKK38PnSHstcupbc09R2W&opi=89978449

Table 21. NDA 214927 Study NPC-002: Summary of TEAEs Affecting ≥8% of Subjects in the Arimoclomol Arm During the Double-Blind Period and 5% More in the Arimoclomol Arm

	Arimoclomol N=34		Placebo N=16		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Any AE	30	(88.2)	13	(81.3)	6.99	(-14.99, 28.96)	
Upper respiratory tract infection	6	(17.6)	1	(6.3)	11.40	(-6.06, 28.86)	
Weight decreased	5	(14.7)	0	(0.0)	14.71	(2.80, 26.61)	
Decreased appetite	3	(8.8)	0	(0.0)	8.82	(-0.71, 18.36)	
Urticaria	3	(8.8)	0	(0.0)	8.82	(-0.71, 18.36)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Arimoclomol" and SAFFL = "Y" (Arimoclomol); TRT02A = "Placebo" and SAFFL = "Y" (Placebo); APERIOD =2 to 2 and TRTEMFL = "" (Adverse Events).
Percentage threshold: Arimoclomol ≥8%.
Risk difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Study discontinuations in NPC-002 due to adverse events assessed as related or possibly related to arimoclomol were limited to hypersensitivity reactions in two subjects (progressive urticaria and angioedema) and progressive creatinine elevation in one subject (without changes in renal function). The clinical and laboratory findings in each of these subjects resolved after discontinuation of arimoclomol.

One subject randomized to arimoclomol died during the DB phase of NPC-002 due to cardiorespiratory arrest in the setting of recent worsening epileptic encephalopathy, dysphagia with malnutrition requiring nasogastric tube placement and pneumonia. The events leading up to, and including, the cardiopulmonary arrest were assessed as unrelated to the study drug.

There was one study discontinuation due to hypertonia and tremor assessed as possibly related to treatment in the NPC-002 OLE. The hypertonia and tremor reportedly resolved after discontinuation of arimoclomol. One additional SAE, proteinuria, was initially assessed as probably related to treatment by the study investigator. The proteinuria was identified 2 weeks prior to a urinary tract infection and resolved when the infection was treated.

Two subjects died during the OLE phase due to a lower respiratory tract infection and aspiration pneumonia respectively. Neither were assessed as related to the study drug.

In summary, there are no significant safety concerns or risks that were identified with the use of arimoclomol in patients with NPC.

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5 Appendix

5.1 Text of Complete Response Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 214927

COMPLETE RESPONSE

Orphazyme A/S
c/o Orphazyme US Inc.
Attention: Abhijit Pangu, RAC
Senior Director, US Regulatory Affairs
180 N La Salle Street, Suite 3475
Chicago, IL 60601

Dear Mr. Pangu:

Please refer to your new drug application (NDA) dated July 17, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for arimoclomol capsules.

We acknowledge receipt of your major amendment dated December 22, 2020, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

You submitted data from a 12-month, randomized, double-blind, placebo-controlled trial together with confirmatory evidence from in vitro, animal and clinical pharmacology data to establish substantial evidence of effectiveness of arimoclomol for the treatment of Neimann-Pick disease Type C (NPC).

We recognize NPC as a rare, serious and life-threatening disease with a high unmet need and no approved therapies. In situations such as this one, we must incorporate regulatory flexibility, while still ensuring there is substantial evidence of effectiveness.

Based upon our review of your submitted data, we are unable to conclude that there is substantial evidence of effectiveness. This conclusion is based on concerns with your 5 domain NPC Clinical Severity Scale (5DNPCCSS) and the weak and contradictory confirmatory evidence of effectiveness, as explained below, which is in the context of a numerically small treatment effect in your trial (treatment difference of about 1 point on a 25 point scale), problematic “hypothetical estimand”, and the lack of statistical significance at the conventional level ($p<0.05$) on our analysis of the 5DNPCCSS using a while-on-treatment estimand.

Reference ID: 4813409

TRIAL NPC-002:

Primary Efficacy Results:

As discussed at the pre-NDA meeting, we have concerns with your hypothetical estimand targeted by your primary efficacy analysis for the 5DNPCCSS endpoint, which yielded a treatment difference of -1.4 points (95% confidence interval -2.8, 0.0; p=0.046). Hypothetical 5DNPCCSS scores after early escape or premature study discontinuation due to adverse events are not clinically plausible (that is, it is not reasonable to assume a hypothetical treatment effect for patients who stopped treatment for a clinical reason, because the expectation in this situation is that, for the same clinical reason, treatment would not be resumed). We also question the appropriateness of the underlying missing at random assumption based on derived estimated means of the missing hypothetical scores conditional on the observed trajectories using your Mixed Model Repeated Measures (MMRM) analysis. Therefore, our main efficacy evaluation focused on the while-on-treatment estimand, where the treatment effect was quantified by the difference between the two treatment arms in the mean change from baseline to 12 months or last visit prior to study treatment discontinuation. In this analysis, the estimated treatment difference was -1.2 (95% confidence interval -2.7, 0.3; p=0.12), which does not meet the conventional threshold for statistical significance ($p<0.05$) and is numerically small relative to the 0 to 25 range for the 5DNPCCSS score. In this context, we have identified the following concerns with the 5DNPCCSS, many of which were communicated at several time points during your IND development, as summarized below.

5DNPCCSS Regulatory History:

In our September 2, 2016, advice letter we indicated that certain domains of the NPCCSS (specifically speech, ambulation, fine motor skills, cognition, memory, and seizures) were either not well-defined or likely insensitive to change, and recommended performance-based assessments to standardize the evaluation of specific domains (cognition, ambulation, fine motor, memory). We restated in an advice letter dated January 19, 2017 that the NPCCSS, in its current form, was not well-defined and reliable, and requested evidence demonstrating that the measurement of the domains of the NPCCSS (i.e., those intended to be included as a primary endpoint) are standardized across patients and sites (e.g., by inclusion of performance tests such as the Scale for the Assessment and Rating of Ataxia or SARA, 9-hole peg test, and neurological examinations), and demonstrating that the NPCCSS scoring was reliable and reproduceable. In a meeting dated July 20, 2017, we reiterated that our earlier advice communicated on September 2, 2016 and January 19, 2017 had not been fully incorporated, and indicated that establishing the validity and standardization of all five domains was needed, especially performance tests for swallowing, cognition, and speech. In a meeting dated July 10, 2019, given that we had not assessed the measurement properties of the 5DNPCCSS prior to trial completion and data

unblinding, we conveyed that the adequacy of the 5DNPCCSS score would be an NDA review issue.

5DNPCCSS Validity Concerns:

- Despite our advice during the IND phase, the NDA did not include data that compares the 5DNPCCSS domains with other measures (e.g., performance-based assessment of neurocognitive functioning, SARA speech and gait subdomains) to help establish the validity of the instrument, with the exception of the American Speech-Language-Hearing Association National Outcomes Measurement System (ASHA-NOMS) Swallow Scale and the Penetration-Aspiration Scale (PAS), discussed below.

- We have several concerns with the swallow domain (which together with speech and fine motor skills accounts for the numerical difference in the 5DNPCCSS endpoint between arimoclomol and placebo). These concerns, described below, raise questions as to whether the swallow score reflects the patient's level of swallowing dysfunction, whether no change in the swallow score reflects a true delay in swallowing dysfunction progression, and whether improvement or worsening of the swallow score reflects actual improvement or worsening of swallowing. Because the 5DNPCCSS total score is calculated by adding the swallow domain score to other scores we are concerned that the issues identified with the swallow domain impact interpretability of the 5DNPCCSS total score.

    - The same swallow score is given for situations that may not be equivalent, such as a "3" for patients who report "coughing while eating + intermittent dysphagia with liquids and solids," "coughing while eating + dysphagia with liquids," or "coughing while eating + dysphagia with solids". A "4" is given for patients who report "nasogastric tube or gastric tube for supplemental feeding," "cough while eating + intermittent dysphagia with liquids + dysphagia with solids," or "cough while eating + intermittent dysphagia with solids + dysphagia with liquids." A score of "5", which represents the most severe presentation could indicate "cough while eating plus dysphagia with solids plus dysphagia with liquids" or "nasogastric tube or gastric tube feeding only." While higher scores are intended to reflect increased disease severity, it is not clear that the scores are ordered to reflect clinical progression in severity.

    - It is uncertain whether the identified issues with the swallow domain will bias results toward the null or away from the null, particularly because this small randomized trial had differences between treatment arms in baseline swallow scores with differential opportunities to show apparent worsening or improvement even if such changes reflected construct-irrelevant variance due to shortcomings with the instrument. For example, there were five arimoclomol patients who improved on their swallow scores, four

with a two-point improvement and one with a one-point improvement. However, the placebo arm had less opportunity to show improvement because 44% of placebo-treated patients had a non-zero score at baseline, with only 38% having high enough baseline scores to allow for a two-point improvement compared to 65% of arimoclomol-treated patients with a non-zero score at baseline. It is also unclear whether the differences in baseline swallowing scores may have led to differential behavioral advice (e.g., to cut food into smaller pieces) across the two treatment arms that could have also impacted the scoring.

- Use of the NIH natural history study to quantitatively evaluate the validity of NPCCSS swallow scores through comparison with scores on the ASHA-NOMS Swallow Scale and the PAS showed positive correlations between the NPCCSS swallow scores and scores on these other scales at baseline and Month 12. However, there was poor alignment between baseline swallow scores on the NPCCSS vs. ASHA-NOMS and PAS (with a considerable number of patients having a normal score on the ASHA-NOMS and PAS but having non-zero scores of 1-4 on the NPCCSS swallow domain). In addition, there was poor alignment between NPCCSS swallow scores in the 0-3 range with the ASHA-NOMS and PAS, which is the region of the response scale in which improvement in swallowing was seen with arimoclomol in Study NPC-002.

- Regarding the other 5DNPCCSS domains, there are several response options that appear problematic. For example, two response options for the ambulation domain involve retrospective reports of early childhood development (e.g., ataxic unassisted gait or not walking by 18 months) that would not be able to change in a drug trial of older patients and do not measure what matters to patients, which is current ambulation ability. For the cognition domain, some of the response options may reflect the patient environment rather than a drug effect (e.g., access to services). Also, cognition is a broad concept and cannot adequately be evaluated using a single item clinician-reported scale. For the fine motor skills domain, the difference between “slight” dysmetria and “mild” dysmetria is unclear.

CONFIRMATORY EVIDENCE:

The confirmatory evidence of effectiveness for arimoclomol appears weak and contradictory, as summarized below:

- In eight cell lines derived from NPC patients, incubation with increasing concentrations of arimoclomol (50 to 400 µM) increased NPC1 protein expression. These in vitro concentrations are 16-fold to more than 130-fold maximal plasma concentrations (~1.5-3 µM) observed with the clinical doses. The clinical relevance of the in vitro findings at these high exposures is unclear.

- There are two non-GLP studies and one GLP study in an (Npc-/-) mouse model of NPC disease. One of the non-GLP studies showed improved ataxia at the low dose but not at the high dose of arimoclomol. This paradoxical finding related to dose is unexpected for a drug effect. In addition, improvement in ataxia was not seen with arimoclomol in the other non-GLP mouse study or in the GLP mouse study. The second non-GLP study showed improved survival with an unexpected increase in brain glycosphingolipid with arimoclomol. You hypothesize that arimoclomol may benefit patients with NPC by upregulating heat shock proteins that could improve intracellular trafficking of cholesterol and glycosphingolipids in patients with NPC. The observed increase in brain glycosphingolipids in this study does not appear consistent with the intended effect of the drug. In addition, there was no improvement in survival with arimoclomol in the GLP study. GLP studies are the gold standard for nonclinical work in terms of documentation and reproducibility, and the lack of any reproducibility in the GLP study is a concern.

- You included your peer-reviewed publication by Kirkegaard et. al.[1] to provide additional nonclinical support for arimoclomol's effectiveness, but it is unclear whether this publication is an aggregation of previous work already included in the NDA, a post-hoc analysis of previous work, independent studies, or a combination of these approaches.

- In Trial NPC-002 eight pharmacodynamic biomarkers were assessed and only one (Lyso-SM-509 at 6 months) demonstrated a significant treatment difference. Although the Lyso-SM-509 data may suggest a possible pharmacologic effect of arimoclomol in NPC patients, the data were not consistent across the 6 and 12 month timepoints and none of the other pharmacodynamic biomarker data showed statistically significant differences between arimoclomol and placebo. Therefore, the submitted biomarker data are not considered adequate to serve as confirmatory evidence. We have outlined several concerns with the data below.

    - HSP70 concentrations in peripheral blood mononuclear cells significantly increased from baseline in the 11 arimoclomol treated patients with available data (nominal p=0.001), but a similar numerical increase was also observed in the four placebo treated patients. The missing data in a significant number of patients limits conclusions.

    - While there appeared to be numerical mean reductions from baseline with arimoclomol compared to placebo on unesterified cholesterol in peripheral blood mononuclear cells and on serum cholestane-triol, there was

[1] Kirkegaard T, Gray J, Priestman DA, et al. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses, Sci Transl Med. 2016: 8(355): 355ra118.

substantial variability in the measurements, and differences between treatment arms were not statistically significant.

- An exploratory analysis of Lyso-SM-509, a novel lipid that is elevated in the plasma of NPC patients showed a significant reduction from baseline at 6 months (p=0.05) that was less pronounced at 12 months (p=0.40). However, the clinical relevance of the reduction in Lyso-SM-509 in NPC patients is not well-understood, and no evidence is provided to demonstrate that reduction in Lyso-SM-509 corresponds with clinical efficacy. In addition, the LC-MS/MS bioanalytical assay used to determine plasma Lyso-SM-509 concentrations has not been fully validated due to lack of sample stability testing.

In summary, we have concerns that the available data do not meet the evidentiary standard for substantial evidence of effectiveness based on the weak and contradictory confirmatory evidence and validity concerns with the 5DNPCCSS in the context of a numerically small treatment effect that was not statistically significant (p=0.12) at the conventional level when using a while-on-treatment estimand.

INFORMATION NEEDED TO RESOLVE THE DEFICIENCIES:

Provide substantial evidence of effectiveness for arimoclomol for the treatment of NPC.

1. Address point-by-point each of the issues identified in this letter regarding the 5DNPCCSS domains and swallow scores, including:

    a. Whether the NPCCSS swallow scores and other domain scores can be improved by rescoring.

    b. The alignment concerns in the NIH natural history study between NPCCSS swallow scores in the 0-3 range with the ASHA-NOMS and PAS, with an explanation for the considerable number of patients in the NIH natural history study who are reported to have a normal ASHA-NOMS and PAS score but who reported dysphagia, with scores of 1-4 on the NPCCSS swallow domain.

    c. When responding to the 5DNPCCSS concerns, include analyses and rationale that addresses whether bias in each of the domain scores and the total score would be towards the null or away from the null.

2. We recommend additional quantitative and qualitative evidence to support the interpretation and use of 5DNPCCSS scores to evaluate arimoclomol's treatment effects. Examples include, but are not limited to, showing that clinicians can clearly and consistently interpret and differentiate the response options within each domain of the 5DNPCCSS (e.g., using a qualitative cognitive interview

study with NPC clinical experts and/or clinical exerts with sufficiently related expertise to address validity questions about the 5DNPCCSS). Additional data providing quantitative validity evidence for each of the 5DNPCCSS domains using established performance-based or clinician-reported outcome measures administered longitudinally concomitantly with the 5DNPCCSS could also be useful.

3. Consider whether there are additional analyses and/or other data that you can provide from Trial NPC-002 that may be able to address any of the identified concerns. Examples include, but are not limited to:

    - Data and analyses of the skin biopsies performed at baseline, month 6, and month 12 of the trial

    - Clinically meaningful changes at the patient level in the trial based on comparisons of Much Improved or Very Much Improved on the Global Impression of Change to the 5DNPCCSS

    - Additional in vitro, nonclinical and/or clinical data that provide a scientific basis for some of the subgroup findings (e.g., whether arimoclomol is ineffective in patients with double-null mutations, and whether there is a pharmacodynamic interaction between arimoclomol and miglustat)

4. We recommend that you bolster the confirmatory evidence of effectiveness to help establish that there is a true drug effect. Examples include, but are not limited to:

    - A short-term, cross-over pharmacodynamic study using sufficiently validated assays in a reasonable number of patients to clearly establish arimoclomol's effects on biomarkers related to its mechanism of action in NPC

    - Other data from Trial NPC-002 (e.g., findings from skin biopsies performed at baseline, 6 months and 12 months in the trial).

This application may need discussion at an advisory committee meeting during the next review cycle.

ADDITIONAL COMMENTS

We also have the following comment that is not an approvability issue:

- Trial NPC-002 only enrolled patients with NPC type 1 but you are seeking approval for all patients with NPC, including those with NPC type 2. Provide a scientific rationale for extending the indication to those with NPC type 2.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[4]

PROPRIETARY NAME

Refer to correspondence dated October 16, 2020, which addresses the proposed proprietary name, Miplyffa. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

---

[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drugmarketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

We strongly recommend that you request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
06/17/2021 06:45:24 PM

Reference ID: 4813409

Summary of Regulatory History Prior to the Original NDA Submission

Table 22. Key Regulatory History Prior to the Original NDA Submission

Date	Interaction	Topic
December 17, 2014	Pre-IND meeting	The Agency provided feedback on overall development program, including study design, nonclinical and clinical pharmacology, and product quality strategy.
January 12, 2016	Pre-IND meeting	Discussion focused on the proposed primary endpoint for their Phase 2/3 trial. Agency raised concerns about the challenges of interpreting a composite scoring of 17 domains in the NPCCSS and the instrument's reliability and validity.
March 4, 2016	FDA/EMA commentary	The Agency and the European Medicines Agency (EMA) issued a common commentary to Orphazyme that reflected alignment in concern over the use of a historical control, the usefulness of a 6-month observational study prior to enrollment, the need to select clinically meaningful endpoints, and the need to standardize raters' training for the NPCCSS as inter-rater reliability was a concern.
June 2, 2016	IND 124547 Safe to Proceed	Initial IND was reviewed and studies NPC-001 (a prospective natural history study) and NPC-002 were deemed safe to proceed.
September 2, 2016 /January 19, 2017	Information Request/ Advice Letter	In follow-up interactions, the Agency expressed concerns regarding their proposed primary endpoint. The Agency suggested that the Applicant focus on the domains that capture the core symptoms/signs of NPC where a meaningful change of improvement can be demonstrated.
July 20, 2017	Type B Meeting	The Applicant proposed a revised primary endpoint of the 5DNPCCSS including ambulation, swallow, fine motor skills, cognition and speech. The Agency expressed that the proposed change is reasonable although the issues identified previously regarding the instrument's validity and scoring standardization had not been addressed.
September 28, 2017	Other Submission	The Applicant submitted Study OR-REL-NPC-01, "A study to assess inter-and-intra-rater reliability of the 5DNPCCSS" (the Agency provided feedback in an advice letter on December 21, 2017).
July 17, 2018	Type C meeting	During discussions regarding the Applicant's statistical analysis plan (SAP), the Agency encouraged the use of the Clinical Global Impression of Change as a coprimary endpoint to anchor the 5DNPCCSS, based on an evolving understanding of the challenges of using individual NPCCSS domains.
July 10, 2019	Type C meeting	The Applicant (Orphazyme) requested input on the completed phase 2/3 of Study NPC-002 and the planned 505(b)(1) NDA submission strategy. The Agency raised concerns with the primary efficacy analyses, safety dataset, and the Applicant's request to defer renal and hepatic impairment studies. The Agency accepted the Applicant's proposal for late submission of the final study reports of the renal and hepatic impairment studies.

Date	Interaction	Topic
March 10, 2020	Type B meeting	Agency clarified that the cardiac QT study could not be deferred until after approval, and that all components of the study would need to be submitted for the NDA review.
April 16, 2020	Pre-NDA meeting	The Agency denied the Applicant's request to further delay the thorough QT (TQT) study report submission. The Applicant's proposed primary estimand for Study NPC-002 was not agreed upon due to concerns that its estimation relied upon hypothetical scores for patients who died, received early escape therapy, or discontinued the study due to arimoclomol-induced adverse events.
July 17, 2020	NDA 214927 submission	NDA 214927 was submitted in 3 parts: (1) CMC modules, (2) nonclinical modules, (3) clinical modules.
December 22, 2020	Final TQT Study Report	The Applicant submitted the final TQT study report late in the review cycle, extending the user fee goal by three months from March 17, 2021 to June 17, 2021.
June 17, 2021	Complete Response	The Agency issued a Complete Response letter on June 17, 2021.

5.2 The NPCCSS As Administered in Study NPC-002

ORPHAZYME

PROTOCOL: CT-ORZY-NPC-002

NPC SEVERITY SCORE

VISIT NUMBER: DATE OF COMPLETION (dd/mmm/yyyy): . . . /. . . . / . . . .

PATIENT NUMBER: DATE OF BIRTH (dd/mmm/yyyy): . . . /. . . . / . . . .

Eye Movement	Score =
Normal eye movement	0
Mild vertical supranuclear gaze palsy (VSGP) detected by physician only	1
Functional VSGP, noted by family or compensation with head movements	2
Total VSGP, abnormal horizontal saccades may be present	3
Total ophthalmoplegia (vertical and horizontal saccades absent)	5
Ambulation	**Score =**
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18 months	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5
Speech	**Score =**
Normal speech	0
Mild dysarthria (easily understood)	1
Severe dysarthria (difficult to understand)	2
Non-verbal/functional communication skills for needs	3
Minimal communication	5
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
Fine Motor Skills	**Score =**
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/Dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for self-care activities)	5

Version 1.0 – 01 Apr 2016 Page 1 of 4

ORPHAZYME

NPC SEVERITY SCORE

VISIT NUMBER: DATE OF COMPLETION (dd/mmm/yyyy): . . . /. . . . / . . . .

PATIENT NUMBER: DATE OF BIRTH (dd/mmm/yyyy): . . . /. . . . / . . . .

Cognition	Score =
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum or modified work setting	3
Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function	4
Minimal cognitive function	5
Hearing	**Score =**
Normal hearing (all tones ≤ 15 dB HL)	0
High frequency hearing loss (PTA** ≤ 15 dB HL, > 15 dB HL in high frequencies)	1
Slight-mild hearing loss (PTA 16–44 dB HL)	2
Moderate hearing loss (PTA 45–70 dB HL)	3
Severe hearing loss (PTA 71–90 dB HL)	4
Profound hearing loss (PTA > 90 dB HL)	5
Memory	**Score =**
Normal	0
Mild short-term or long-term memory loss	1
Moderate short-term or long-term memory loss (gets lost)	2
Difficulty following commands	3
Unable to follow commands or short- and-long-term memory loss	4
Minimal memory	5
Seizures	**Score =**
No history of seizures	0
Hx of single seizure	1
Rare seizures	2
Seizures, well controlled with meds	3
Seizures, difficult to control with meds	5

**Score is additive within these two subsections*

***PTA = pure-tone average-reported on the audiogram*

Modifiers	
Gelastic cataplexy	**Score =**
No history	0
Definitive history	+1
Frequent (every month)	+2
Hyperreflexia	**Score =**
None	0
Mild (3+)	+1
Severe (+ clonus)	+2
Narcolepsy	**Score =**
No history	0
Definitive history	+1
Frequent (every month)	+2
Incontinence	**Score =**
No problems	0
Occasional	+1
Frequent	+2
Behavior	**Score =**
No problems	0
Hx of ADHD, aggressive	+1
Harmful to self/others	+2
Auditory Brainstem Response (ABR)	**Score =**
Normal	0
Abnormal	+1
Absent	+2
Psychiatric	**Score =**
No problems	0
Hx of mild depression	+1
Hx of major depression, hallucinations, or psychotic episodes	+2
Respiratory	**Score =**
No problems	0
Hx pneumonia	+1
Pneumonia ≥ 2x/y ear or active therapeutic intervention	+2

PROTOCOL: CT-ORZY-NPC-002

NPC SEVERITY SCORE

VISIT NUMBER: DATE OF COMPLETION (dd/mmm/yyyy): . . . /. . . . /. . . .

PATIENT NUMBER: DATE OF BIRTH (dd/mmm/yyyy): . . . /. . . . /. . . .

Name of the person completing the Score: _____

Study Role: _____

Site number: _____

Signature: _____

Date (dd/mmm/yyyy): _____

IN CASE OF NEW FINDING(S), PLEASE COMPLETE:

Name of the reviewer: _____

Study Role: _____

Site number: _____

Signature: _____

Date (dd/mmm/yyyy): _____

Source: Applicant's COA Evidence Dossier Version 4.0 Dated 26 May 2020, Appendix C
Abbreviations: ADHD, attention deficit hyperactive disorder; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale

5.3 Additional Information for Study NPC-002

5.3.1 Criteria for Early Escape

To fulfill early escape criteria, the protocol prespecified three of the five domains in the 5DNPCCSS as "relevant" (ambulation, fine motor and swallow). Early escape from Study NPC-002 was allowed when patients met one of the following criteria:

Either

- Criterion 1: An increase of at least 2 points simultaneously in two of the three relevant domains of the NPCCSS (for at least 4 points in total) within a period of 3 months;

Or

- Criterion 2: An increase of 3 points simultaneously in two out of the three relevant domains of the NPCCSS (for at least 6 points in total) within a period of 6 months;

Or

- Criterion 3: An increase of at least 2 points simultaneously in all three relevant domains of the NPCCSS (for at least 6 points in total) within a period of 6 months.

5.3.2 Scoring of Key NPCCSS Domains

Table 23. Scoring of Key NPCCSS Domains

Item	Scoring			Min-Max Score[a]
Ambulation	0 = Normal 1 = Clumsy 2 = Ataxic unassisted gait or not walking by 18 months 4 = Assisted ambulation or not walking by 24 months 5 = Wheelchair dependent			0–5
Fine Motor Skills	0 = Normal 1 = Slight dysmetria/dystonia (independent manipulation) 2 = Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty) 4 = Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self) 5 = Severe dysmetria/Dystonia (gross motor limitation, requires assistance for self-care activities)			0–5
Swallow	Response category	Rescored	Original	0-5
	Normal, no dysphagia	0	0	
	Cough while eating	1	1	
	Intermittent dysphagia with liquids	2	2	
	Intermittent dysphagia with solids	2	2	
	Intermittent dysphagia with liquids + solids	2	3	
	Dysphagia with liquids	3	3	
	Dysphagia with solids	3	3	
	Dysphagia with liquids + intermittent dysphagia with solids	3	4	
	Intermittent dysphagia with liquids + dysphagia with solids	3	4	
	Dysphagia with liquids + solids	3	5	
	Nasogastric tube or gastric tube for supplemental feeding	4	4	
	Nasogastric tube or gastric tube feeding only	5	5	
Cognition	0 = Normal 1= Mild learning delay, grade appropriate for age 3 = Moderate learning delay, individualized curriculum or modified work setting 4 = Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function 5 = Minimal cognitive function			0–5
Speech	0 = Normal 1 = Mild dysarthria (easily understood) 2 = Severe dysarthria (difficult to understand) 3 = Non-verbal/functional communication skills for needs 5 = Minimal communication			0–5
5-domain NPCCSS (5DNPCCSS)	Sum of all scores of the following domains with original Swallow domain: Ambulation, Fine Motor Skills, Swallow (original), Speech, Cognition			0–25[b]
Rescored 4-domain NPCCSS (R4DNPCCSS)	Sum of all scores of the following domains with rescored Swallow domain: Ambulation, Fine Motor Skills, Swallow (rescored), Speech			0-20

[a] higher score = more severe clinical impairment
NPCCSS = NPC Clinical Severity Scale
Source: (Patterson et al., 2021)[M5.3.5.4 COA Dossier, Appendix C]; [M1.11.3 COA Evidence Summary Report, Table 13].

Source: NDA 214927 Summary of Clinical Efficacy in Resubmission (Table 3, page 22).

5.3.3 FDA Concerns Regarding Hypothetical Estimand in Original Submission

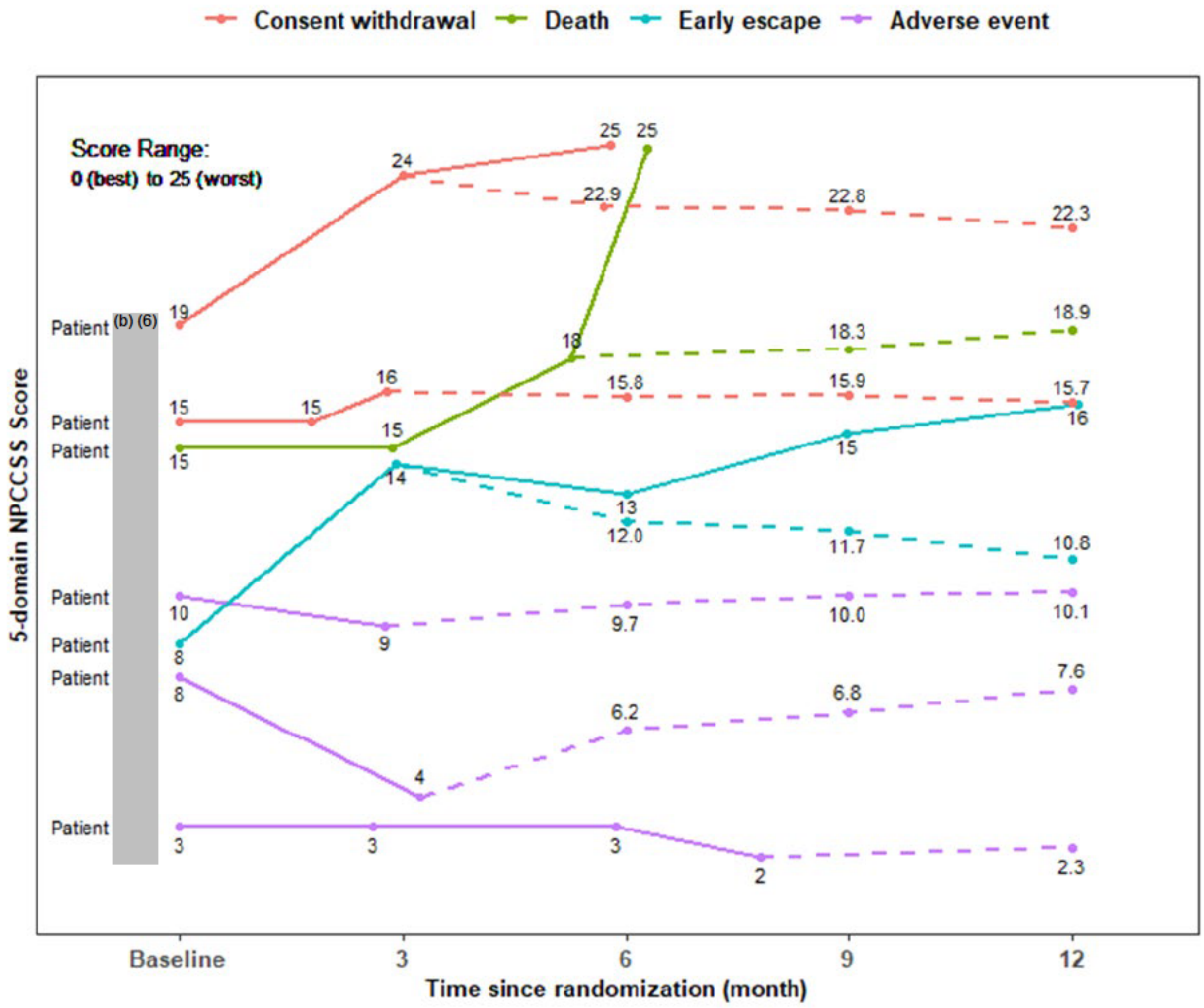
The prespecified primary MMRM analysis in the original submission estimated a treatment effect under the hypothetical scenario (referred to in this document as the “hypothetical strategy”) that all randomized patients in the study adhered to their blinded treatments through month 12. From the FDA’s perspective, such a hypothetical scenario where all randomized patients adhered to their blinded

treatment through 12 months despite clinical reasons leading to treatment discontinuation is of no clinical interest. The expectation in the clinical practice for patients who stopped treatment for a clinical reason is that the same treatment would not be resumed for the same clinical reason.

In addition, the FDA questioned the appropriateness of the Missing-At-Random (MAR) assumption of the prespecified MMRM analysis targeting the hypothetical treatment effect. The MAR assumption of the MMRM analysis implies that the conditional distribution (i.e., mean and standard deviation) of a missing hypothetical score given observed data can be reasonably estimated. However, based on the FDA's evaluation of the Applicant's MMRM analysis, the appropriateness of the MAR assumption is questionable. Specifically, the FDA derived the estimated means of the missing hypothetical scores conditional on the observed trajectories using the Applicant's MMRM for the patients who prematurely discontinued the study or took the early escape route in the arimoclomol arm (see the section "FDA's Approach to Understand Handling of Missing Values in MMRM" below for technical details). In Figure 36, the dashed lines present the estimated conditional means of the missing hypothetical scores based on the Applicant's MMRM given the observed trajectories. The following are the key observations that appear unreasonable, which make us question the appropriateness of the MAR assumption:

- Patient (b) (6) in the arimoclomol arm who took the early escape route and received open-label arimoclomol after Month 3: the observed score at 12 months was 16 points while the estimated mean of the hypothetical score at 12 months by the Applicant's analysis given this patient's observed trajectory was 10.8 points. This implies that if this patient had continued to be treated with blinded arimoclomol rather than with open-label arimoclomol after early escape, this patient would have improved to 10.8 points rather than the observed worsening to 16 points. Given the identical treatment received after escape with the exception of maintenance of blinding to the arimoclomol treatment, such a difference appears to be unrealistic.
- Patient (b) (6) who died: the last observed score was 25 points, which is the worst score possible. The last observed score of 25 was excluded from the Applicant's analysis as this was obtained at an unscheduled visit. The estimated mean of the hypothetical score at 12 months by the Applicant's analysis given this patient's observed trajectory is 18.9 points, under the hypothetical scenario that this patient had not died and continued to be treated with arimoclomol.

Figure 36. Five-Domain NPCCSS Score for Discontinued or Early Escape Patients



Source: FDA.
Solid lines, observed 5-domain NPCCSS scores; dashed lines, estimated means of hypothetical 5DNPCCSS scores by the Applicant's MMRM models if the subjects in the figure adhered to their blinded treatments.
Abbreviations: MMRM, mixed methods for repeated measures; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale

Table 24 presents the primary analysis results of the primary endpoint in the original submission. The estimated treatment difference in the while-on-treatment estimand was -1.17 (95% CI: -2.65, 0.31; p-value =0.1184) numerically favoring the arimoclomol arm. The estimated treatment difference in the treatment-policy estimand ranges from -0.90 to -0.95 depending on the methods for handling missing data.

Table 24. Summary of 5-Domain NPCCSS Score

Parameter	Arimoclomol	Placebo	Difference (95% CI)	p-value
Score at Baseline	N=34	N=16		
Mean (SD)	12.1 (6.9)	9.4 (6.4)		
Median (min, max)	11.5 (2.0, 24.0)	8.0 (0.0, 24.0)		
Score at 12 months	N=28	N=15		
Mean (SD)	13.1 (7.8)	11.5 (7.7)		
Median (min, max)	13.0 (1.0, 25.0)	10.0 (0.0, 25.0)		
Change from baseline at 12 months	N=28	N=15		
Mean (SD)	1.0 (2.3)	2.0 (3.0)		
Median (min, max)	0.0 (-2.0, 8.0)	1.0 (-1.0, 11.0)		
Estimated estimands, mean (SE)				
Applicant's hypothetical estimand[1]	0.72 (0.40)	2.12 (0.55)	-1.40 (-2.76, -0.03)	0.0456
Agency's while-on-treatment estimand[2]	0.99 (0.41)	2.16 (0.60)	-1.17 (-2.65, 0.31)	0.1184
Agency's treatment-policy estimand[3]				
Method 1 (worst change)	1.17 (0.40)	2.13 (0.58)	-0.95 (-2.39, 0.48)	0.1860
Method 2 (placebo median)	1.27 (0.40)	2.18 (0.58)	-0.90 (-2.34, 0.53)	0.2107
Method 3 (multiple imputation)	1.29 (0.42)	2.19 (0.61)	-0.90 (-2.37, 0.56)	0.2269

Source: FDA's analyses.
[1] Estimated mean change (SE) from baseline to 12 months by the Applicant's MMRM.
[2] Estimated mean change (SE) from baseline at 12 months or last visit prior to study discontinuation by the Agency's ANCOVA model adjusted for baseline 5DNPCCSS score and miglustat use.
[3] Estimated mean change (SE) from baseline at 12 months by the Agency's ANCOVA model adjusted for baseline 5DNPCCSS score and miglustat use; Method 1 used the worst change within each patient; Method 2 used the maximum value between the worst change within each patient and the median change (1.0) in the placebo group; Method 3 used multiple imputation based on the observed distribution of change from baseline to 12 months in the placebo group.
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

5.3.4 Summary of Individual Domains in 5DNPCCSS

Table 25 presents a summary of individual domains in 5DNPCCSS. Overall, the mean baseline score is higher in the arimoclomol arm compared to the placebo arm for all five domains. The estimated treatment differences in the 5DNPCCSS score endpoint appear to be driven by the swallow, speech, and fine motor skills domains. The observed mean change from baseline to 12 months was lower for the arimoclomol arm compared to the placebo arm for these three domains: swallow (0.1 versus 0.6), speech (-0.1 versus 0.3), and fine motor skills (0.3 versus 0.6). For the other two domains, the mean change from baseline to 12 months was higher for the arimoclomol arm compared to the placebo arm: ambulation (0.4 versus 0.3), and cognition (0.3 versus 0.1).

Table 25. Summary of Individual Domains in 5DNPCCSS

Domain	Arimoclomol	Placebo	Difference (95%CI)	p-value
Swallow				
Score at baseline	N=34	N=16		
Mean (SD)	1.9 (1.7)	1.3 (1.7)		
Median (min, max)	2.0 (0.0, 5.0)	0.0 (0.0, 4.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	0.1 (1.1)	0.6 (1.0)		
Median (min, max)	0.0 (-2.0, 3.0)	0.0 (0.0, 3.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.23 (0.20)	0.57 (0.29)	-0.34 (-1.06, 0.37)	0.3387
Treatment-policy[2]	0.29 (0.19)	0.57 (0.28)	-0.28 (-0.97, 0.40)	0.4115

Domain	Arimoclomol	Placebo	Difference (95%CI)	p-value
Rescored Swallow				
Score at baseline	N=34	N=16		
Mean (SD)	1.8 (1.6)	1.1 (1.4)		
Median (min, max)	2.0 (0.0, 5.0)	0.0 (0.0, 4.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	0.1 (1.1)	0.7 (1.1)		
Median (min, max)	0.0 (-2.0, 3.0)	0.0 (0.0, 3.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.12 (0.20)	0.63 (0.29)	-0.51 (-1.24, 0.21)	0.1633
Treatment-policy[2]	0.18 (0.19)	0.63 (0.29)	-0.45 (-1.15, 0.25)	0.2004
Speech				
Score at baseline	N=34	N=16		
Mean (SD)	2.2 (1.6)	1.6 (1.2)		
Median (min, max)	2.0 (0.0, 5.0)	1.0 (0.0, 5.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	-0.1 (1.0)	0.3 (0.8)		
Median (min, max)	0.0 (-3.0, 2.0)	0.0 (0.0, 3.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.01 (0.16)	0.30 (0.23)	-0.30 (-0.86, 0.27)	0.2993
Treatment-policy[2]	0.04 (0.16)	0.30 (0.23)	-0.26 (-0.83, 0.30)	0.3507
Fine Motor Skills				
Score at baseline	N=34	N=16		
Mean (SD)	2.8 (1.8)	1.9 (1.8)		
Median (min, max)	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	0.3 (0.9)	0.6 (1.3)		
Median (min, max)	0.0 (-1.0, 3.0)	0.0 (0.0, 5.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.27 (0.16)	0.49 (0.23)	-0.22 (-0.79, 0.36)	0.4494
Treatment-policy[2]	0.30 (0.15)	0.48 (0.23)	-0.18 (-0.74, 0.38)	0.5272
Ambulation				
Score at baseline	N=34	N=16		
Mean (SD)	2.5 (1.6)	2.2 (1.6)		
Median (min, max)	2.0 (0.0, 5.0)	1.5 (0.0, 5.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	0.4 (0.7)	0.3 (0.9)		
Median (min, max)	0.0 (0.0, 3.0)	0.0 (-1.0, 3.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.34 (0.12)	0.33 (0.17)	0.01 (-0.40, 0.42)	0.9554
Treatment-policy[2]	0.34 (0.12)	0.33 (0.17)	0.01 (-0.40, 0.42)	0.9554

Domain	Arimoclomol	Placebo	Difference (95%CI)	p-value
Cognition				
Score at baseline	N=34	N=16		
Mean (SD)	2.8 (1.3)	2.5 (1.5)		
Median (min, max)	3.0 (0.0, 4.0)	3.0 (0.0, 5.0)		
Change at 12 months	N=28	N=15		
Mean (SD)	0.3 (0.5)	0.1 (0.6)		
Median (min, max)	0.0 (0.0, 2.0)	0.0 (-1.0, 2.0)		
Estimated mean (SE) change				
While-on-treatment[1]	0.29 (0.11)	0.13 (0.16)	0.16 (-0.23, 0.56)	0.4022
Treatment-policy[2]	0.35 (0.10)	0.13 (0.14)	0.22 (-0.12, 0.56)	0.1903

Source: FDA's analyses.
[1] Estimated mean change from baseline using the while-on-treatment strategy.
[2] Estimated mean change from baseline using the treatment-policy strategy (Method 2 in Tables 6 and 7 for handle missing data).
Abbreviations: CI, confidence interval; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SD, standard deviation; SE, standard error

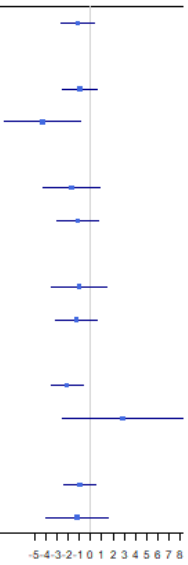
5.3.5 Subgroup Analyses of Primary Endpoint

Table 26 presents the results of subgroup analyses by age at baseline, age at first neurological symptoms, sex, miglustat use, and baseline score for the 5DNPCCSS endpoint, respectively. These subgroup analyses were performed using the while-on-treatment strategy. The general patterns observed in Table 26 remain the same with the treatment-policy strategy.

The subgroup analyses numerically consistently favor the arimoclomol arm except the subgroup of subjects who were not on miglustat use.

Table 26. Analyses of 5DNPCCSS Score in Subgroups by Age, Age at First Neurological Symptoms, Sex, Miglustat Use, and Baseline Score

Subgroup	Arimoclomol N / Mean	Placebo N / Mean	Difference (95% CI)
Overall	34 / 0.99	16 / 2.16	-1.2 (-2.7, 0.3)
Age at baseline			
< 12 years	16 / 1.43	11 / 2.38	-0.9 (-2.5, 0.6)
>= 12 years	18 / -0.10	5 / 4.18	-4.3 (-7.6, -0.9)
Age at first neuro symptom			
< 2 years	6 / 0.99	3 / 2.68	-1.7 (-4.3, 0.9)
>= 2 years	28 / 0.95	13 / 2.10	-1.1 (-2.9, 0.6)
Sex			
Female	17 / 0.88	9 / 1.89	-1.0 (-3.5, 1.5)
Male	17 / 1.13	7 / 2.40	-1.3 (-3.1, 0.5)
On miglustat			
Yes	26 / -0.21	13 / 1.89	-2.1 (-3.5, -0.7)
No	8 / 5.23	3 / 2.39	2.8 (-2.5, 8.2)
Baseline score			
<= 8	13 / 0.29	9 / 1.24	-0.9 (-2.4, 0.5)
> 8	21 / 1.59	7 / 2.81	-1.2 (-3.9, 1.5)



Source: FDA's analysis. For each subgroup, the estimated mean change from baseline to 12 months or last visit prior to study discontinuation and its difference (95% CI) were obtained from ANCOVA models. The ANCOVA models were adjusted for baseline 5DNPCCSS score and miglustat use for the subgroups by age, age at first neurological symptoms, sex, and baseline 5DNPCCSS. The ANCOVA models for subgroups by miglustat use was adjusted for baseline 5-domain NPCCSS score.
Abbreviations: CI, confidence interval; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale

Table 27. Baseline Demographics by Baseline Use of Miglustat

	On Miglustat		Not on Miglustat	
Variable	**Arimoclomol N=26**	**Placebo N=13**	**Arimoclomol N=8**	**Placebo N=3**
Age, years				
Mean (SD)	12.8 (4.68)	9.1 (3.62)	7.0 (5.37)	15.0 (1.73)
Median	14.0	9.0	5.5	16.0
IQR	10.0, 16.0	8.0, 11.0	3.0, 10.0	13.0, 16.0
Min, max	2.0, 19.0	3.0, 16.0	2.0, 17.0	13.0, 16.0
Age at first neurological symptoms, years				
Mean (SD)	5.2 (3.34)	4.0 (3.20)	4.4 (3.87)	10.3 (1.53)
Median	4.5	3.0	3.5	10.0
IQR	3.2, 7.0	2.0, 5.0	1.9, 6.0	9.0, 12.0
Min, max	0.2, 14.2	1.0, 11.0	0.0, 12.3	9.0, 12.0
Double functional null, n (%)				
Yes	0	0	3 (37.5)	0
No	26 (100)	13 (100)	5 (62.5)	3 (100)
Sex, n (%)				
Female	14 (53.8)	8 (61.5)	3 (37.5)	1 (33.3)
Male	12 (46.2)	5 (38.5)	5 (62.5)	2 (66.7)

	On Miglustat		Not on Miglustat	
Variable	Arimoclomol N=26	Placebo N=13	Arimoclomol N=8	Placebo N=3
Race, n (%)				
Asian	1 (3.8)	1 (7.7)	0	0
Native Hawaiian or Other Pacific Islander	0	1 (7.7)	0	0
Unknown	1 (3.8)	1 (7.7)	0	0
White	24 (92.3)	10 (76.9)	8 (100.0)	3 (100.0)
Country, n (%)				
Denmark	1 (3.8)	2 (15.4)	0	0
France	2 (7.7)	2 (15.4)	1 (12.5)	0
Germany	6 (23.1)	3 (23.1)	0	0
Italy	4 (15.4)	1 (7.7)	1 (12.5)	0
Poland	0	1 (7.7)	5 (62.5)	3 (100.0)
Spain	2 (7.7)	1 (7.7)	0	0
Switzerland	1 (3.8)	1 (7.7)	0	0
United Kingdom	7 (26.9)	2 (15.4)	0	0
United States	3 (11.5)	0	1 (12.5)	0

Source: FDA's table.
Abbreviation: SD, standard deviation

Table 28. Summary of R4DNPCCSS Score by Baseline Use of Miglustat in Study NPC-002

	On Miglustat		Not on Miglustat	
Parameter	Arimoclomol	Placebo	Arimoclomol	Placebo
Score at Baseline	N=26	N=13	N=8	N=3
Mean (SD)	8.9 (6.1)	7.0 (5.8)	10.1 (5.1)	5.3 (0.6)
Median (min, max)	7.5 (1.0, 20.0)	5.0 (0.0, 19.0)	11.0 (2.0, 17.0)	5.0 (5.0, 6.0)
Score at 12 months	N=22	N=12	N=6	N=3
Mean (SD)	9.1 (6.7)	9.1 (7.2)	12.7 (5.9)	7.3 (1.2)
Median (min, max)	9.0 (0.0, 20.0)	6.5 (0.0, 20.0)	12.5 (4.0, 20.0)	8.0 (6.0, 8.0)
Change at 12 months[1]				
Mean (SD)	-0.2 (1.0)	1.9 (3.4)	3.5 (2.8)	2.0 (1.7)
Median (min, max)	0.0 (-2.0, 2.0)	1.0 (0.0, 12.0)	2.0 (1.0, 8.0)	3.0 (0.0, 3.0)
Estimated change[2]				
While-on-treatment				
Mean (SE)	-0.39 (0.40)	1.85 (0.57)	4.13 (0.96)	1.98 (1.66)
Difference (95% CI)		-2.24 (-3.65, -0.82)		2.15 (-2.46, 6.77)
p-value		0.0028		0.3129
Treatment-policy[3]				
Mean (SE)	-0.07 (0.40)	1.90 (0.57)	4.13 (0.96)	1.98 (1.66)
Difference (95% CI)		-1.97 (-3.39, -0.55)		2.15 (-2.46, 6.77)
p-value		0.0080		0.3129

Source: FDA's analyses.
[1] Change from baseline at 12 months.
[2] Estimated mean change: estimated mean change from baseline.
[3] Method 2 in Tables 7 and 8 is used to handle missing data.

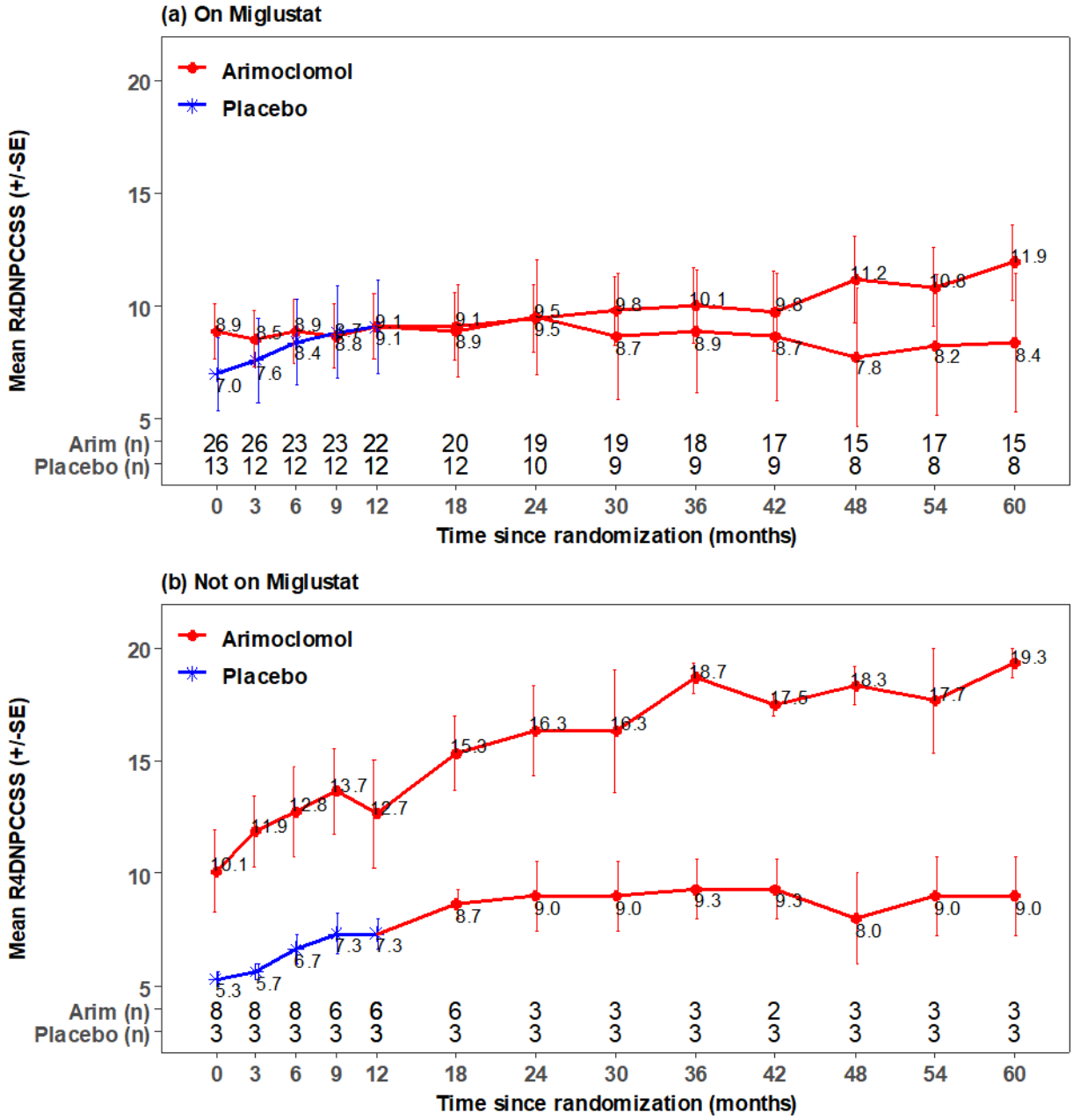
Table 29. Data Listing for Subjects Who Did Not Use Miglustat at Baseline in Study NPC-002

SUBJID	Treatment Arm	Double Function Null Genotype	Baseline Age	Age of Onset of Neurological Symptoms	4DNPCCSS		COUNTRY
					Baseline	CHG[1]	
(b) (6)	Arimoclomol	Y	3	0.00	14	6	ITA
	Arimoclomol	Y	2	0.75	2	2	FRA
	Arimoclomol	Y	3	3.00	14	6	POL
	Arimoclomol	N	4	3.00	5	8	POL
	Arimoclomol	N	7	4.00	7	2	POL
	Arimoclomol	N	7	6.00	12	6	USA
	Arimoclomol	N	13	6.00	17	1	POL
	Arimoclomol	N	17	12.3	10	2	POL
	Placebo	N	13	9.00	6	0	POL
	Placebo	N	16	10.0	5	3	POL
	Placebo	N	16	12.0	5	3	POL

Source: FDA's analysis.

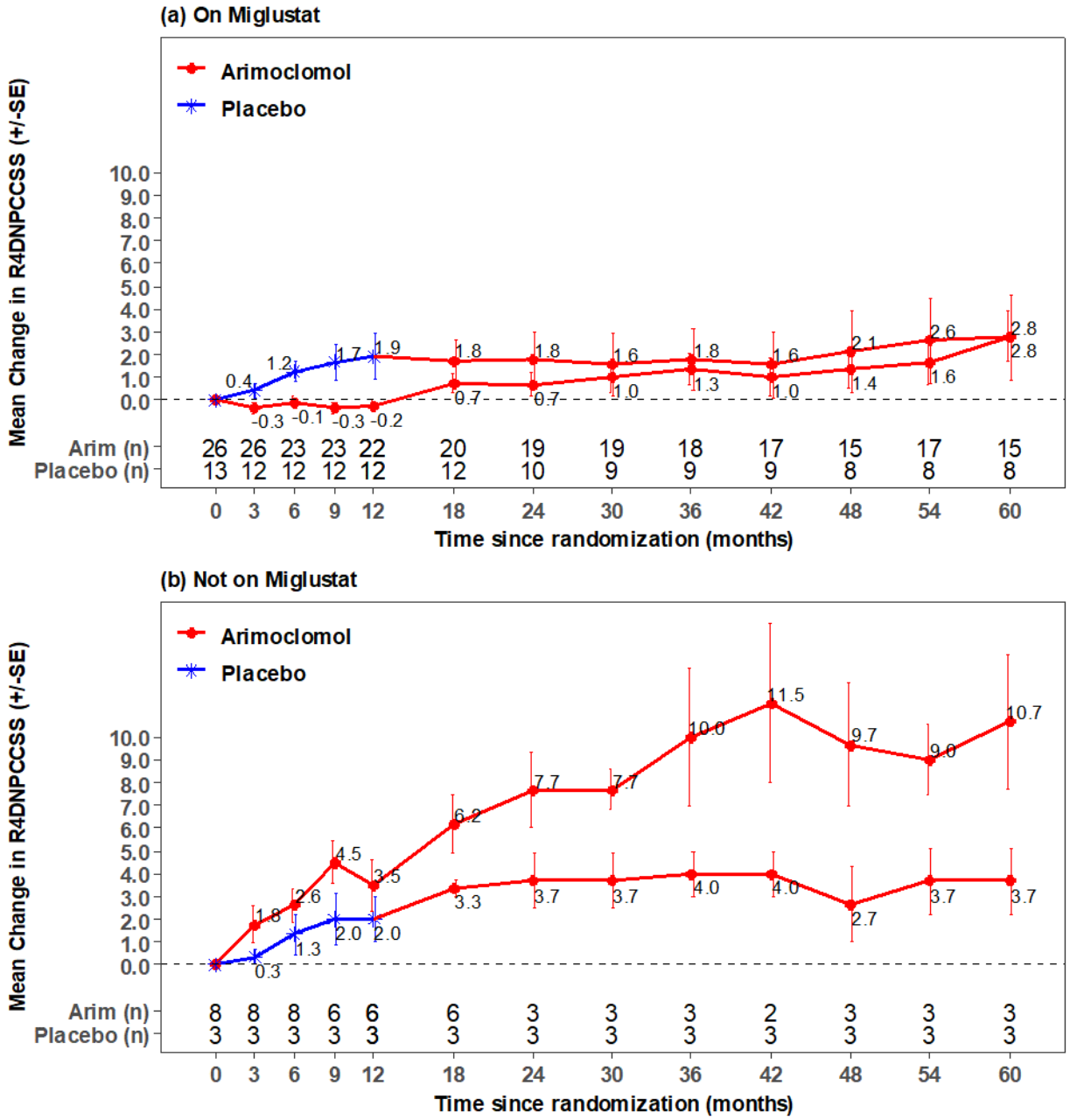
[1] CHG: Change from baseline at 12 months or the last study visit prior to 12 months.

Figure 37. Mean R4DNPCCSS Score Over Time by Miglustat Use Subgroups in Study NPC-002



Source: FDA's figures. The rows 'Arim (n)' and 'Placebo (n)' present the number of patients in the arimoclomol arm and in the placebo arm, respectively.
Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SE, standard error

Figure 38. Mean Change From Baseline in R4DNPCCSS Score Over Time by Miglustat Use Subgroups in Study NPC-002



Source: FDA's figure. The rows 'Arim (n)' and 'Placebo (n)' present the number of patients in the arimoclomol arm and in the placebo arm, respectively.
Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale; SE. standard error

5.3.6 Efficacy Results of Key Secondary Endpoints

The protocol-defined key secondary endpoints are as follows:

- Responder analysis of patient's CGI-I score remains stable or shows improvement at 12 months (for the United States Food and Drug Administration [FDA] submission, this endpoint is considered a coprimary endpoint);

- Responder analysis of patient's 5-domain NPCCSS score remains stable or improves at 12 months compared to baseline;
- Time to worsening (as defined by reaching the minimal clinically important difference [MCID] of 2 points compared to baseline on 5-domain NPCCSS [5DNPCCSS]);
- Proportion of patients worsening (as defined by reaching the MCID of 2 points compared to baseline on 5DNPCCSS) at 6 and 12 months;
- Change in full scale NPCCSS score apart from hearing domains (i.e., Hearing and Auditory Brainstem Response) at 12 months.

Table 30 presents the results of the key secondary endpoints.

Table 30. Summary of Results for Key Secondary Endpoints

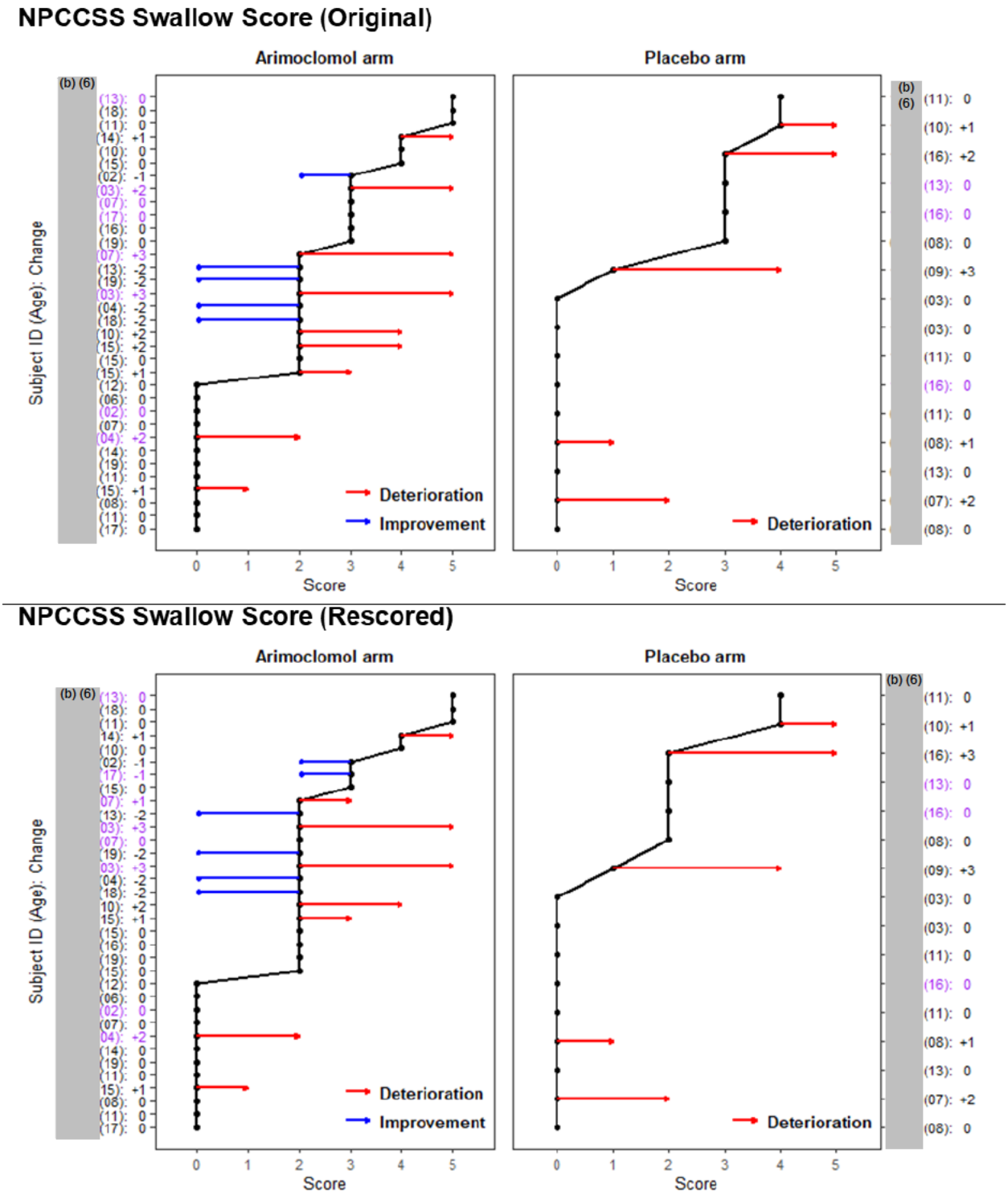
Endpoints	Arimoclomol (N=34)	Placebo (N=16)	Difference (95% CI)	p-value
Responder in CGI-I at 12 months, n (%)	20 (58.8%)	9 (56.3%)	-	1.0000[1]
Responder in 5DNPCCSS at 12 months, n (%)	17 (50.0%)	6 (37.5%)	-	0.5456[1]
Time to worsening, months				
25th percentile	5.2	5.5	-	0.8021[2]
Median	12.7		-	
Proportion of worsening				
6 months, n (%)	12 (35.3%)	8 (50.0%)	-	0.3662[3]
12 months, n (%)	15 (44.1%)	7 (43.8%)	-	1.0000[3]
Change in full NPCCSS[4]				
6 months, mean (SE)	0.7 (2.6)	2.1 (5.0)	-1.69 (-4.04, 0.66)[4]	0.1546[4]
12 months, mean (SE)	1.20 (2.7)	2.7 (5.4)	-1.61 (-4.24, 1.01)[4]	0.2199[4]

Source: Section 11.2 of the Clinical Study Report.
[1] p-value obtained from chi-squared test.
[2] p-value obtained from log-rank test stratified by miglustat use.
[3] p-values obtained from Fisher's exact test.
[4] Difference (95% CI) and p-values obtained from ANCOVA models including baseline score and miglustat use as covariates.
Abbreviations: CI, confidence interval; SD, standard deviation

5.3.7 Impact of Swallow Rescoring

Figure 39 depicts change from baseline in NPCCSS swallow domain at 12 months or last visit in the DB phase. The black dots represent the baseline NPCCSS swallow score. Red lines represent deterioration from baseline while blue lines represent improvement from baseline. The length of the lines indicates the magnitude of changes. The labels in the vertical axis in each panel presents subject ID (age) followed by change from baseline. The patients colored in purple were the patients who were not using miglustat at baseline. Table 31 presents the subjects whose change from baseline to 12 months (or last visit prior to the DB phase) in swallow domain were impacted by the rescoring.

Figure 39. Swallow Domain Score at Baseline and 12 Months (or Last Visit in Double-Blind Phase)



Source: FDA's figure.
For the scoring system of the swallow domain, see Table 23
Abbreviations: NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

Table 31. Change From Baseline to Month 12 (or Last Visit Prior to DB Phase) Impacted by Rescoring of the Swallow Domain

Arimoclomol Group				
ID	**Baseline Category**	**Category at Month 12 or Last Visit**	**Change From Baseline**	
			Original	**Rescored**
(b) (6)	Cough while eating / intermittent dysphagia with liquids	(Month 3) Cough while eating / intermittent dysphagia with liquids / intermittent dysphagia with solids	1	0
	Cough while eating / intermittent dysphagia with liquids	(Month 12) Cough while eating / dysphagia with liquids / intermittent dysphagia with solids	2	1
	Cough while eating / dysphagia with liquids	(Month 12) Cough while eating / Intermittent dysphagia with liquids / Intermittent dysphagia with solids	0	-1
	Cough while eating / intermittent dysphagia with liquids / intermittent dysphagia with solids	(Month 6) Nasogastric tube or gastric tube feeding only	2	3
	Cough while eating / intermittent dysphagia with liquids	(Month 6) Cough while eating / dysphagia with liquids / dysphagia with solids	3	1
Placebo Group				
ID	**Baseline Category**	**Category at Month 12 or Last Visit**	**Change From Baseline**	
			Original	**Rescored**
(b) (6)	Cough while eating / intermittent dysphagia with liquids / intermittent dysphagia with solids	(Month 12) Nasogastric tube or gastric tube feeding only	2	3

Source: FDA's analysis.
Abbreviations: DB, double-blind

5.3.8 Percentage Change From Baseline at 12 Months in R4DNPCCSS

As exploratory analyses, we investigated the endpoint of percent change from baseline at 12 months in R4DNPCCSS for the overall population (Table 32) and by miglustat use status (Table 33). These analyses yielded a similar conclusion as the analyses for the endpoint of change from baseline: the point estimates for the treatment difference numerically favor the arimoclomol arm.

Table 32. Percentage Change From Baseline to Month 12 in R4DNPCCSS in Study NPC-002

Parameter	Arimoclomol	Placebo	Difference (95% CI)	p-value
Score at baseline	N=34	N=16		
Mean (SD)	9.2 (5.8)	6.7 (5.2)		
Median (min, max)	8.5 (1.0, 20.0)	5.0 (0.0, 19.0)		
Score at 12 months	N=28	N=15		
Mean (SD)	9.9 (6.6)	8.7 (6.5)		
Median (min, max)	9.5 (0.0, 20.0)	7.0 (0.0, 20.0)		
Percentage change from baseline at 12 months	N=28	N=15		
Mean (SD)	1.7 (49.6)	30.9 (42.2)		
Median	0.0	20.0		
Min, max	-100.0, 160.0	0.0, 150.0		
Estimated percentage change from baseline at 12 months, mean (SE)				
Agency's while-on-treatment estimand[1]	-0.61 (6.88)	32.60 (10.11)	-33.21 (-58.06, -8.37)	0.0099
Agency's treatment-policy estimand[2]				
Method 1 (worst change)	2.79 (6.82)	31.90 (10.02)	-29.12 (-53.76, -4.48)	0.0216
Method 2 (placebo median)	5.80 (7.03)	32.53 (10.33)	-26.73 (-52.14, -1.32)	0.0396

Source: FDA's analyses.

[1] Estimated mean percentage change (SE) from baseline at 12 months or last visit prior to study discontinuation by the Agency's ANCOVA model adjusted for baseline 5DNPCCSS score and miglustat use.

[2] Estimated mean percentage change (SE) from baseline at 12 months by the Agency's ANOCVA model adjusted for baseline 5DNPCCSS score and miglustat use; Method 1 used the worst change within each patient; Method 2 used the maximum value between the worst change within each patient and the median change in the placebo group.

Only one subject in the placebo arm had a baseline score of zero for R4DNPCCSS. Since this subject had a zero score at all post-baseline visits, the percentage change endpoint was calculated as zero in all 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

Table 33. Percentage Change From Baseline to Month 12 in R4DNPCCSS by Subgroups of Miglustat Use in Study NPC-002

	On Miglustat		Not on Miglustat	
Parameter	**Arimoclomol**	**Placebo**	**Arimoclomol**	**Placebo**
Score at baseline	N=26	N=13	N=8	N=3
Mean (SD)	8.9 (6.1)	7.0 (5.8)	10.1 (5.1)	5.3 (0.6)
Median	7.5	5.0	11.0	5.0
Min, max	1.0, 20.0	0.0, 19.0	2.0, 17.0	5.0, 6.0
Score at 12 months	N=22	N=12	N=6	N=3
Mean (SD)	9.1 (6.7)	9.1 (7.2)	12.7 (5.9)	7.3 (1.2)
Median	9.0	6.5	12.5	8.0
Min, max	0.0, 20.0	0.0, 20.0	4.0, 20.0	6.0, 8.0
Percent Change at 12 months[1]				
Mean (SD)	-14.0 (33.5)	28.6 (44.9)	59.6 (59.0)	40.0 (34.6)
Median	0.0	12.6	35.7	60.0
Min, max	-100.0, 20.0	0.0, 150.0	5.9, 160.0	0.0, 60.0
Estimated mean percent change[2]				
While-on-treatment				
Mean (SE)	-17.14 (6.82)	28.95 (9.69)	65.51 (13.54)	15.36 (23.35)
Difference (95% CI)		-46.09 (-70.24, -21.94)		50.16 (-14.90, 115.22)
p-value		0.0004		0.1133
Treatment-policy[3]				
Mean (SE)	-10.87 (6.99)	29.28 (9.93)	68.30 (14.07)	16.97 (24.27)
Difference (95% CI)		-40.14 (-64.89, -15.39)		51.33 (-16.31, 118.96)
p-value		0.0022		0.1182

Source: FDA's analyses.
[1] Percentage change from baseline at 12 months.
[2] Estimated mean percent change: estimated mean percent change from baseline.
[3] Method 2 in Tables 7 and 8 is used to handle missing data.
Only one subject in the placebo arm had a baseline score of zero for R4DNPCCSS. Since this subject had a zero score at all post-baseline visits, the percentage change endpoint was calculated as zero in all analyses.

5.3.9 FDA's Approach to Understand Handling of Missing Values in MMRM

This subsection provides details of the FDA's approach to understand how the missing values of the primary endpoint were handled in the SAP-defined mixed model for repeated measures (MMRM) analysis.

Let y_{it} be the change from baseline in the 5DNPCCSS score at time t for subject i with $t = 1, 2, 3,$ or 4 indicating month 3, 6, 9, or 12, respectively. Let $\boldsymbol{Y_i}$ be a $t_i \times 1$ vector containing observed change from baseline for subject i at t_i time points. For example, if the change from baseline for subject i was obtained at months 3 and 6 and missed at months 9 and 12, $\boldsymbol{Y_i}$ is defined as follows: $\boldsymbol{Y_i} = (y_{i1}, y_{i2})^T$. The SAP-defined MMRM analysis assumes that the $\boldsymbol{Y_i}$ follows the model

$$\boldsymbol{Y_i} = \boldsymbol{X_i}\boldsymbol{\beta} + \boldsymbol{e_i},$$

where $\boldsymbol{X_i}$ is a $t_i \times p$ known matrix of the covariates, $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown regression parameters, and the $\boldsymbol{e_i}$ is a $t_i \times 1$ residual random vector following a multivariate normal distribution

$\boldsymbol{N}(\mathbf{0}, \boldsymbol{\Sigma_i})$. The MMRM model further assumes that $\boldsymbol{\Sigma_i}$ is a submatrix of a 4×4 matrix $\boldsymbol{\Sigma}$. The log-likelihood λ for the observed data ($\boldsymbol{Y_1}$, …, $\boldsymbol{Y_n}$) is given as

$$\lambda = Const. - \frac{1}{2}\sum_{i=1}^{n} log|\boldsymbol{\Sigma_i}| - \frac{1}{2}\sum_{i=1}^{n}(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T \ \boldsymbol{\Sigma_i}^{-1}(\boldsymbol{Y_i} - \boldsymbol{X_i\beta}).$$

The MMRM model finds a pair of ($\boldsymbol{\beta}$, $\boldsymbol{\Sigma}$) maximizing the log-likelihood λ. If there are no missing data (i.e., change from baseline is obtained at all 4 time points for all subjects), a closed mathematical form of ($\boldsymbol{\beta}$, $\boldsymbol{\Sigma}$) maximizing λ exists. However, in the presence of missing data, λ needs to be maximized by a numerical algorithm. In the literature, several numerical algorithms have been developed to find a maximizer of λ. The majority of them are iterative algorithms where $\boldsymbol{\beta}$ is updated given a current estimate of $\boldsymbol{\Sigma}$ and then $\boldsymbol{\Sigma}$ is updated given the updated $\boldsymbol{\beta}$.

The review team focused on the expectation-maximization (EM) algorithm developed by (Jennrich and Schluchter 1986) for repeated-measures models. The EM algorithm consists of two parts as follows:

- The first part updates $\boldsymbol{\beta}$ while holding $\boldsymbol{\Sigma}$ fixed.
- The second part updates $\boldsymbol{\Sigma}$ while holding $\boldsymbol{\beta}$ fixed. The update of $\boldsymbol{\Sigma}$ is performed using a generalized EM algorithm by (Dempster 1977), as illustrated below.

Let $\boldsymbol{Y_i^*} = (y_{i1}, y_{i2}, y_{i3}, y_{i4})^T$ be the complete response data for subject i. Recall that $\boldsymbol{Y_i}$ is the observed part of $\boldsymbol{Y_i^*}$. Let $\boldsymbol{Y_{i,miss}}$ be the missed part of $\boldsymbol{Y_i^*}$. For example, if the change from baseline for subject i was obtained at months 3 and 6 and missed at months 9 and 12, then $\boldsymbol{Y_i} = (y_{i1}, y_{i2})^T$, $\boldsymbol{Y_{i,miss}} = (y_{i3}, y_{i4})^T$, and $\boldsymbol{Y_i^*} = (\boldsymbol{Y_i}, \boldsymbol{Y_{i,miss}})^T$. Similarly, let $\boldsymbol{X_i^*} = (\boldsymbol{X_i}, \boldsymbol{X_{i,miss}})^T$ be the design matrix for the complete response data.

The second part of the EM algorithm to update $\boldsymbol{\Sigma}$ proceeds as follows:

- Step 1: The likelihood λ is reconstructed with the complete data. Specifically, the log-likelihood λ for the complete data ($\boldsymbol{Y_1^*}$, …, $\boldsymbol{Y_n^*}$) is given as

$$\lambda = Const. - \tfrac{1}{2}\textstyle\sum_{i=1}^{n} log|\boldsymbol{\Sigma_i}| - \tfrac{1}{2}\sum_{i=1}^{n}(\boldsymbol{Y_i^*} - \boldsymbol{X_i^*\beta})^T \ \boldsymbol{\Sigma_i}^{-1}(\boldsymbol{Y_i^*} - \boldsymbol{X_i^*\beta})$$

$$= Const. - \frac{1}{2}\sum_{i=1}^{n} log|\boldsymbol{\Sigma_i}| - \frac{1}{2}\sum_{i=1}^{n} trace\{\boldsymbol{\Sigma_i}^{-1}\boldsymbol{A_i}\},$$

where

$$\boldsymbol{A_i} = \begin{bmatrix} (\boldsymbol{Y_i} - \boldsymbol{X_i\beta})(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T & (\boldsymbol{Y_i} - \boldsymbol{X_i\beta})(\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})^T \\ (\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T & (\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})(\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})^T \end{bmatrix}.$$

- Step 2 (expectation step): $\boldsymbol{A_i}$ is replaced with its conditional expectation (denoted by $\boldsymbol{A_i^*}$) given $\boldsymbol{Y_i}$, $\boldsymbol{X_i^*}$, $\boldsymbol{\beta}$, and the current estimate of $\boldsymbol{\Sigma}$. See (Dempster 1977) and (Jennrich and Schluchter 1986) for additional details. For example, the component $(\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T$ of $\boldsymbol{A_i}$ is replaced by the following:

$$\boldsymbol{E}\{(\boldsymbol{Y_{i,miss}} - \boldsymbol{X_{i,miss}\beta})(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma}\} = \{\boldsymbol{E}(\boldsymbol{Y_{i,miss}}|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma}) - \boldsymbol{X_{i,miss}\beta}\}(\boldsymbol{Y_i} - \boldsymbol{X_i\beta})^T.$$

By comparing $\boldsymbol{A_i^*}$ to $\boldsymbol{A_i}$, one can see that the missing values ($\boldsymbol{Y_{i,miss}}$) are replaced with $\boldsymbol{E}(\boldsymbol{Y_{i,miss}}|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma})$ in this algorithm. The term $\boldsymbol{E}(\boldsymbol{Y_{i,miss}}|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma})$ is the estimated mean of the missing hypothetical scores conditional on the observed trajectories. This term can be viewed as "implicitly imputed values of missing data" in the EM algorithm. This term is often referred to as predicted values of missing values from the model given observed data.

- Step 3 (maximization step): The likelihood obtained at Step 2 (by replacing $\boldsymbol{A_i}$ with $\boldsymbol{A_i^*}$) is maximized with respect to $\boldsymbol{\Sigma}$.
- Step 4: Steps 2 and 3 are repeated until numerical convergence of $(\boldsymbol{\beta}, \boldsymbol{\Sigma})$.

By using the multivariate normal theory, one can show that the implicitly imputed values of missing data, denoted by $\boldsymbol{E}(\boldsymbol{Y_{i,miss}}|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma})$, can be given as follows:

$$\boldsymbol{E}(\boldsymbol{Y_{i,miss}}|\boldsymbol{Y_i}, \boldsymbol{X_i^*}, \boldsymbol{\beta}, \boldsymbol{\Sigma}) = \boldsymbol{X_{i,miss}\beta} + \boldsymbol{\Sigma_{21}\Sigma_{11}^{-1}}(\boldsymbol{Y_i} - \boldsymbol{X_i\beta}),$$

where $\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma_{11}} & \boldsymbol{\Sigma_{12}} \\ \boldsymbol{\Sigma_{21}} & \boldsymbol{\Sigma_{22}} \end{pmatrix}$, $\boldsymbol{\Sigma_{11}} = cov(\boldsymbol{Y_i})$, $\boldsymbol{\Sigma_{22}} = cov(\boldsymbol{Y_{i,miss}})$, and $\boldsymbol{\Sigma_{12}} = cov(\boldsymbol{Y_i}, \boldsymbol{Y_{i,miss}})$.

The implicitly imputed values of missing values presented in Figure 36 were derived using the equation above with $\boldsymbol{\beta}$ and $\boldsymbol{\Sigma}$ being the final estimates from the EM algorithm.