ZEVRA THERAPEUTICS

ARIMOCLOMOL FOR TREATMENT OF NIEMANN-PICK DISEASE TYPE C

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

SPONSOR BRIEFING DOCUMENT

GENETIC METABOLIC DISEASES ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
4D-NPCCSS	4-domain Niemann-Pick disease, type C Clinical Severity Scale (ambulation, fine motor skills, speech, and updated swallow)
5D-NPCCSS	5-domain Niemann-Pick disease, type C Clinical Severity Scale (ambulation, fine motor skills, speech, swallow, and cognition)
9-HPT	Nine-Hole Peg Test
AE	Adverse event
AESI	Adverse event of special interest
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASHA-NOMS	American Speech-Language-Hearing Association National Outcomes Measurement System
AST	Aspartate aminotransferase
AUC	Area under the concentration curve
CI	Confidence interval
CLEAR	Coordinated lysosomal expression and regulation
ClinRO	Clinician-reported outcome
CNS	Central nervous system
CRL	Complete Response Letter
CYP	Cytochrome P450
DB	Double-blind
DNA	Deoxyribonucleic acid
EAP	Expanded Access Program
EMA	European Medical Agency
Endo H	Endoglycosidase H
ER	Endoplasmic reticulum
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GD	Gaucher disease
GSL	Glycosphingolipid
HED	Human equivalent dose
Hsp70	Heat shock protein 70
IBM	Inclusion Body Myositis
IND	Investigational New Drug
IPTW	Inverse probability of treatment weighting
LOESS	Locally estimated scatterplot smoothing
MBP	Myelin basic protein
MCID	Minimum clinically important difference
MMRM	Mixed effects model for repeated measurement
MOA	Mechanism of action
mRNA	Messenger ribonucleic acid
NDA	New Drug Application
NIH	National Institutes of Health
NPC	Niemann-Pick disease, type C
NPC1	Niemann-Pick disease, type C intracellular cholesterol transporter 1
NPC2	Niemann-Pick disease, type C intracellular cholesterol transporter 2
Npc1$^{-/-}$	Niemann-Pick disease, type C1-independent (double functional null *Npc1* genotype)
Npc1^{nmf164}	Niemann-Pick disease, type C1-dependent (homozygous D1005G *Npc1* genotype)
NPC-cdb	Niemann-Pick Disease, Type C Clinical Database
NPCCSS	Niemann-Pick disease, type C Clinical Severity Scale

Abbreviation	Definition
OLE	Open-label extension
PAS	Penetration-Aspiration Scale
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARA	Scale for Assessment and Rating of Ataxia
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
TFE3	Transcription factor E3
TFEB	Transcription factor EB
t.i.d.	Three times daily
ULN	Upper limit of normal
US	United States
VFSS	Video fluoroscopic swallowing study
WT	Wild type

1. Executive Summary

1.1 Introduction

Niemann-Pick disease, type C (NPC) is an ultra-rare, severely debilitating neurodegenerative lysosomal storage disease whose hallmark clinical complication is progressive encephalopathy via neuronal death that culminates with patients experiencing uncontrolled seizures, inability to move or communicate, and ultimately fatal dementia or early death due to neurological dysfunction-related comorbidities, such as aspiration-related pneumonias (Walterfang et al., 2012). Although NPC can manifest at any age, it is usually diagnosed in early childhood, and the estimated median age of death is 13 years (Bianconi et al., 2019; Sections 2.1.1 and 2.1.3). There are no FDA-approved therapies for NPC, a disease that uniformly places a tremendous burden on patients, families, and caregivers. The incidence of NPC is approximately 1:100,000 live births in the United States (US), where it affects an estimated 600–900 patients (Geberhiwot et al., 2018; Burton et al., 2021).

NPC results from mutations in the *NPC1* (~95% of cases) or *NPC2* (~5% of cases) genes. Patients with a double functional null mutation usually have very rapid disease progression (Section 2.1.2). Diminished function of either gene causes lysosomal intracellular transport dysfunction, resulting in cholesterol accumulation in lysosomes and a myriad of negative downstream consequences, including cell stress, toxicity, and death. Organs most affected by cholesterol buildup in lysosomes include the liver, spleen, and brain, with progressive neurodegeneration of the brain driving most clinical complications and disability.

1.2 Unmet Need

Despite decades of research and development, there are no FDA-approved therapies for patients with NPC, and there are no established biomarkers correlated with disease severity or survival (Section 2.2.1). At all ages, patients experience a variety of heterogeneous and progressively disabling neurological symptoms that can require frequent hospitalizations (Imrie et al., 2007; Vanier, 2010). However, younger age of onset predicts more rapid disease progression (Patterson et al., 2012). In all cases, patients in the terminal stage cannot communicate, have total ophthalmalgia, and are bedridden due to severe encephalopathy and uncontrolled seizures.

The current treatment paradigm for NPC relies largely on symptomatic management, including anti-seizure medications, spasticity medications, baclofen, and care from a multidisciplinary team. The substrate reduction therapy miglustat is considered part of routine clinical care for NPC worldwide but must be prescribed off-label to treat NPC in the US where it is only indicated for the treatment of a different lysosomal storage disorder, type 1 Gaucher disease (Berry-Kravis, 2021; Zavesca® USPI, 2020).

The profound impact of NPC on patients and their caregivers cannot be overstated. With its relentlessly progressive effect on a patient's daily function, quality of life, and life expectancy, in addition to the heavy burden on caregivers and families, there is an urgent unmet medical need for effective and safe pharmacological interventions.

1.3 Product Description

Zevra Therapeutics is seeking approval of arimoclomol for the treatment of adult and pediatric patients (≥ 2 years) with NPC.

Arimoclomol is an orally bioavailable small molecule that is administered in capsules developed to support ingestion in a population comprising pediatric patients and patients with swallowing difficulties. The capsules can be swallowed whole, or the contents can be emptied into liquid or sprinkled onto soft food. The recommended dose is weight-adjusted and administered three times per day (t.i.d.; Table 6; Section 3.2).

Arimoclomol has a novel mechanism of action (MOA), which targets two fundamental pathways of NPC etiology. Arimoclomol's effects are reversible upon discontinuation, and because it is not a gene therapy, does not affect the patient's genetic makeup. Details on the MOA of arimoclomol in the NPC disease state are described in Section 3.3.1.3.

1.4 Development Program for Arimoclomol for NPC

1.4.1 Program History

Arimoclomol has been granted Orphan Drug Designation, Fast Track Designation, Breakthrough Therapy, and Rare Pediatric Disease Designation by the Food and Drug Administration (FDA) for the treatment of NPC.

A New Drug Application (NDA) was previously submitted for this indication by the drug's original Sponsor, and the current application represents a resubmission with substantial changes and new investigations in alignment with clinical analyses and nonclinical supporting evidence recommended by the FDA. The original NDA was submitted by Orphazyme, Inc. in July 2020 (Figure 1). In that application the pivotal randomized, double-blind, placebo-controlled, Phase 2/3 clinical trial, Study 002, met its prespecified primary efficacy endpoint, and some supportive nonclinical data were submitted.

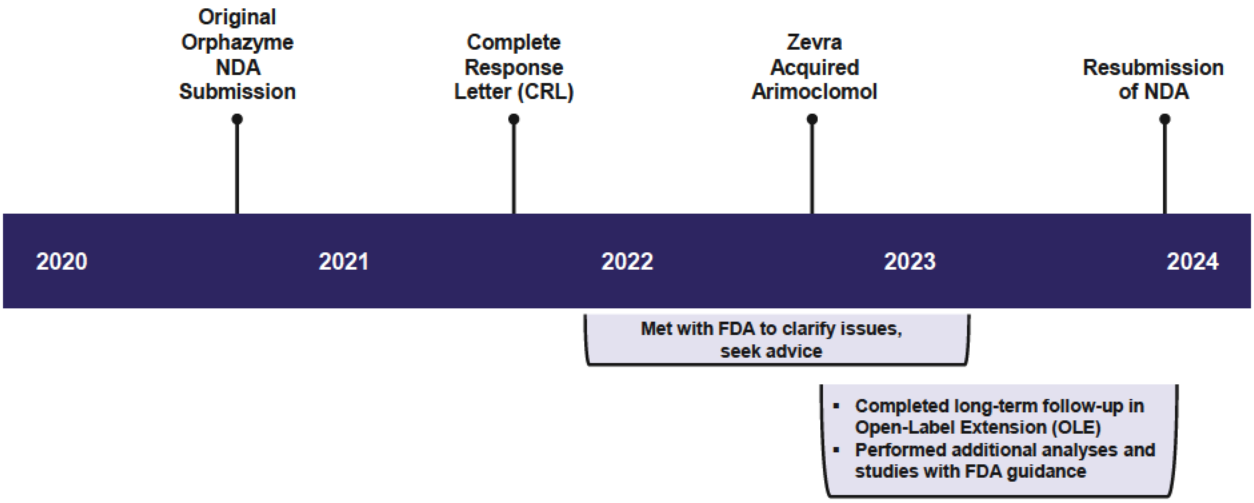
In June 2021, FDA issued a Complete Response Letter (CRL) to Orphazyme, which outlined deficiencies and recommendations to address them. The key issues included in the CRL can be grouped into three categories:

1. Validity and reliability of the 5-Domain NPC Clinical Severity Score (5D-NPCCSS) instrument used as the primary endpoint (See Sections 1.4.3 and 6.5.1 for details.)
2. Appropriateness of the estimand used for the primary efficacy analysis (See Section 6.6.4 for detailed discussion of estimands.)
3. Robustness of confirmatory evidence (See Section 4.3 for an overview nonclinical studies and Section 7 for findings from confirmatory in vitro [Section 7.2.1] and in vivo [Section 7.2.2] studies).

Approximately one year later, in 2022, Zevra Therapeutics acquired arimoclomol from Orphazyme, and completed the open-label extension (OLE) phase of Study 002. Three meetings have been held with FDA to discuss preliminary data and solicit ongoing advice in order to address the issues identified in the CRL.

In December 2023, Zevra resubmitted the NDA with amendments that included new clinical data, revised analyses, and additional supporting nonclinical confirmatory evidence, which together addressed the deficiencies raised by the FDA, as shown in Table 1. The resubmission includes results from the completed 4-year OLE phase of Study 002, eight additional in vitro studies, and three additional in vivo studies, all 11 of which were conducted to strengthen the confirmatory evidence and characterize arimoclomol's MOA in greater detail.

Figure 1: Timeline of Arimoclomol Regulatory History



CRL = complete response letter; NDA = new drug application; OLE = open-label extension.

Table 1: Summary of Actions Taken to Resolve Issues from Complete Response Letter

CRL Issue	Actions to Resolve Issue
1. Concerns with the Validity/ Reliability of NPCCSS	• Removed cognition domain from the 5-Domain endpoint, as agreed with the FDA, and updated results using the 4-Domain NPCCSS endpoint (i.e., ambulation, fine motor skills, speech, updated swallow domain) as the primary endpoint. o A systematic review of the scoring methodology for the swallow domain was carried out in consultation with disease and swallow experts in a qualitative study. The scoring algorithm of the swallow domain was subsequently optimized to reflect linearity of dysfunction, to consolidate scores for presentations with equivalent clinical severity, and to score those with the most severe swallowing dysfunction appropriately (additional details provided in Section 6.5.1). o Analyses of the convergent validity of the NPCCSS swallow domain based on data from the NIH natural history cohort, as well as other requested analyses supporting strong correlations with other endpoints. o Correlation analyses between scores of the NPCCSS ambulation, fine motor skills, and speech domains with relevant performance tests supporting the validity of these three domains. • Addressed study procedure questions.
2. Issues with the Primary Statistical Analysis	• Used FDA-recommended while-on-treatment estimand, demonstrating a statistically significant and clinically meaningful treatment difference for the primary endpoint of 4D-NPCCSS in favor of arimoclomol compared to placebo (p=0.0413; Section 6.8.4.1). Result was consistent with the prespecified analysis using a hypothetical estimand, which estimated treatment effect as if all patients had strictly adhered to treatment through the end of follow-up (p=0.0456). • Provided additional sensitivity analyses to support demonstration of clinical efficacy (Section 6.8.4.2).

CRL Issue	Actions to Resolve Issue
3. Insufficient Confirmatory Evidence of Effectiveness	Submitted new clinical (Section 7.1) and nonclinical (Section 7.2) data, including but not limited to: • Analysis of untreated patients who switched to arimoclomol, either from the observational study or from placebo patients in the double-blind phase of the pivotal trial, showed a meaningful treatment effect as demonstrated by the slowing of disease progression after switching to arimoclomol (Section 7.1.3.2). • Analysis of patients from the OLE phase vs a matched NIH natural history cohort also demonstrated a slower rate of disease progression with arimoclomol treatment (Section 7.1.3.3). • Nonclinical PD data (Section 7.1) showed upregulation of CLEAR genes (Section 7.2.1.2), increased NPC1 protein levels (Section 7.2.1.3), and a corresponding reduction in lipid burden, indicating improved lysosomal function (Section 7.2.1.4). • NPC mouse model studies (Section 7.2.2) showed increases in NPC1 protein levels (Section 7.2.2.4) and positive effects on survival and functional endpoints (Section 7.2.2.2).

CLEAR = coordinated lysosomal expression and regulation; EAP = Expanded access Program; FDA = Food and Drug Administration; NIH = National Institutes of Health; NPCCSS = Niemann-Pick disease, type C Clinical Severity Scale; OLE = open-label extension; PD = pharmacodynamic.

1.4.2 NPC Clinical Program

The NPC clinical program consists of two studies.

Study 001 was an observational natural history study of 36 patients with NPC, which provided information on NPC disease progression over 6 to 14 months. Patients completing Study 001 were eligible for enrollment into the pivotal, placebo-controlled Study 002 (Sections 1.5 and 6.3). A total of 27 (75.0%) patients from Study 001 continued into Study 002.

Study 002 was the pivotal Phase 2/3 study of 50 patients with NPC conducted to evaluate efficacy and safety of arimoclomol for the treatment of NPC. Study 002 consisted of a 1-year placebo-controlled, double-blind treatment period followed by a 4-year OLE phase, during which all patients received arimoclomol. In the double-blind phase of Study 002, patients were randomized 2:1 to receive arimoclomol or placebo. Thirty-four (34; 68.0%) pediatric patients received arimoclomol dosages based on body weight targeting exposure levels approximately equivalent to those achieved in adults at a dose of 372 mg/day. Sixteen patients received placebo. A total of 41 patients received arimoclomol in the OLE phase.

The 12-month period represented the minimum duration expected to be necessary to demonstrate a treatment effect. Additionally, parents of young children with NPC have unequivocally communicated their unwillingness to risk subjecting their children to a placebo for > 1 year.

Results from the arimoclomol clinical development program for the treatment of NPC demonstrate clinically meaningful slowing of NPC disease progression with a safe and well-tolerated therapy through 5 years.

1.4.3 Endpoints in Clinical Studies

There are only two instruments created and used specifically for the clinical study of NPC: the Niemann-Pick, Type C Clinical Severity Scale (NPCCSS; Sections 1.4.3.1 and 6.5.1.1) and the Niemann-Pick, Type C Clinical Database (NPC-cdb; Sections 1.4.3.2 and 6.5.1.2).

Given the extreme rarity of NPC, in addition to the limited natural history documentation before Study 001, the Sponsor selected several additional endpoints that are commonly used for the study of neurological and movement disorders or to assess specific symptoms and generate as comprehensive a data set as possible. However, none of these additional instruments are NPC specific or validated for the disease. Additionally, some measures have minimal utility in younger age groups or patients with severe disease.

1.4.3.1 Niemann-Pick, Type C Clinical Severity Scale (NPCCSS)

The NPCCSS is an NIH-developed, disease-specific, clinician-reported outcome (ClinRO) assessment tool that specifically assesses clinical severity and measures disease progression across 17 domains in patients with NPC (see Section 6.5.1 for complete details).

The original NDA submission for Studies 001 and 002 used and validated the abbreviated 5-domain NPCCSS (5D-NPCCSS) as the primary endpoint. The 5 domains include: ambulation, fine motor skills, speech, swallow, and cognition (Patterson et al., 2021; Yanjanin et al., 2010; Shin et al., 2011; Megias-Vericat et al., 2017; Ory et al., 2017; Cortina-Borja et al., 2018).

Based on FDA recommendations, the analyses in the NDA resubmission were performed with a 4-domain NPCCSS (4D-NPCCSS), in which the cognition domain has been removed and the ambulation, fine motor skills, speech, and swallow domains remain. Domains assessed in the 4D-NPCCSS were determined based on FDA feedback and include an updated scoring methodology for the swallow domain that was applied to the original data collected during the blinded phase of the pivotal trial. (See Figure 16 and Table 10 in Section 6.5.1.1 for detailed comparison of NPCCSS instruments and scoring criteria.)

To score the NPCCSS, clinicians evaluated the patient's clinical symptoms and assigned a score of 0 to 5 in each domain, based on defined criteria. The 4D-NPCCSS total score ranges from 0 to 20 points, with higher scores representing more severe clinical impairment. A 1-point difference in the score constitutes a clinically meaningful change in condition for a patient with NPC. Details on the minimum clinically important difference (MCID) are provided in Section 6.5.1.1.2.

1.4.3.2 Niemann-Pick, Type C Clinical Database (NPC-cdb)

The Niemann-Pick disease, type C Clinical Database (NPC-cdb) per-patient score equals a severity-weighted sum of 72 symptoms across 10 categories: visceral signs, development, motor function, ocular-motor abnormalities, seizures/cataplexy/narcolepsy, cognitive abilities and memory, behavioral and psychiatric abnormalities, speech, hearing, and abilities in daily life (Stampfer et al., 2013). The NPC-cdb patient history questionnaire is administered only at baseline while the NPC-cdb current status questionnaire is used to track progression at each visit. The total score for each questionnaire reflects the patient's historical and current disease severity, respectively.

For Studies 001 and 002, the current-status questionnaire was simplified to facilitate data collection. Each symptom contributed a score ranging from 1 to 5 with a maximum score of 125 points for the total scale.

1.5 Clinical Efficacy Findings from Randomized Controlled Phase 2/3 Study 002

1.5.1 Study 002 Patient Population

A total of 50 patients were randomized 2:1 to arimoclomol (N=34) or placebo (N=16) and were included in the Study 002 Full Analysis Set (FAS; Figure 17; Section 6.8). Demographics and baseline characteristics, including age, sex, race, and body mass index were representative of children and adolescents with NPC (Table 16; Section 6.8.2). Baseline 4D-NPCCSS scores (SE) were higher in the arimoclomol group 9.2 (5.8) vs placebo 6.7 (5.2). All three patients with the rapidly progressing double functional null *NPC1* mutation were randomized to arimoclomol. These patients are unable to produce any viable NPC1 protein.

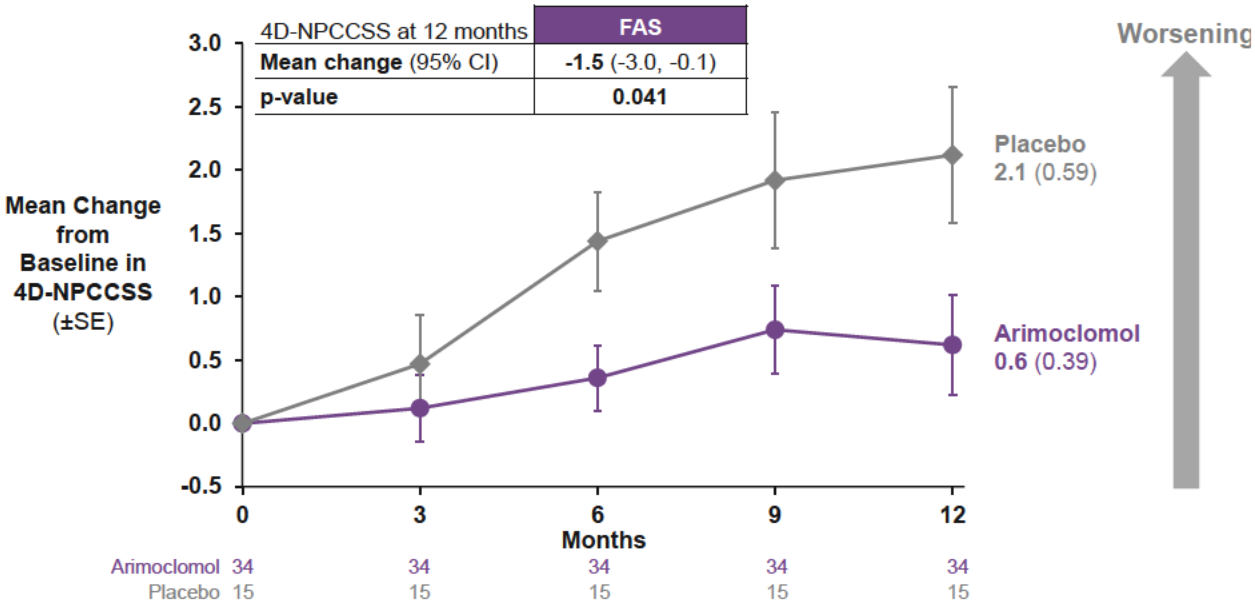
1.5.2 Study 002 Primary Endpoint Results

On the primary endpoint, patients receiving arimoclomol in Study 002 had a clinically meaningful and statistically significant treatment effect vs placebo, as measured by change in 4D-NPCCSS scores between baseline and last visit, using the FDA-recommended while-on-treatment estimand (Figure 2; Table 18; Section 6.8.4.1).

Patients randomized to arimoclomol experienced a slower rate of disease progression during the double-blind phase compared to placebo. Importantly, the arimoclomol group included more patients with severe disease at baseline, including three patients with the rapidly progressing double null *NPC1* mutations vs no placebo patients. (See Section 6.8.3 for additional details.)

Patients receiving arimoclomol demonstrated a clinically meaningful treatment effect at 12 months or last visit while on treatment compared to placebo: the mean change in 4D-NPCCSS score from baseline (SE) was 0.62 (0.39) vs 2.12 (0.59) for arimoclomol vs placebo, respectively, resulting in a statistically significant (p=0.0413) mean treatment difference (95% CI) of -1.51 (-2.95, -0.06) in favor of arimoclomol. The treatment effect was robust, as confirmed by multiple sensitivity analyses (Figure 18; Section 6.8.4.2).

Figure 2: Study 002: 4D-NPCCSS by Study Visit – Double-blind Phase (FAS)



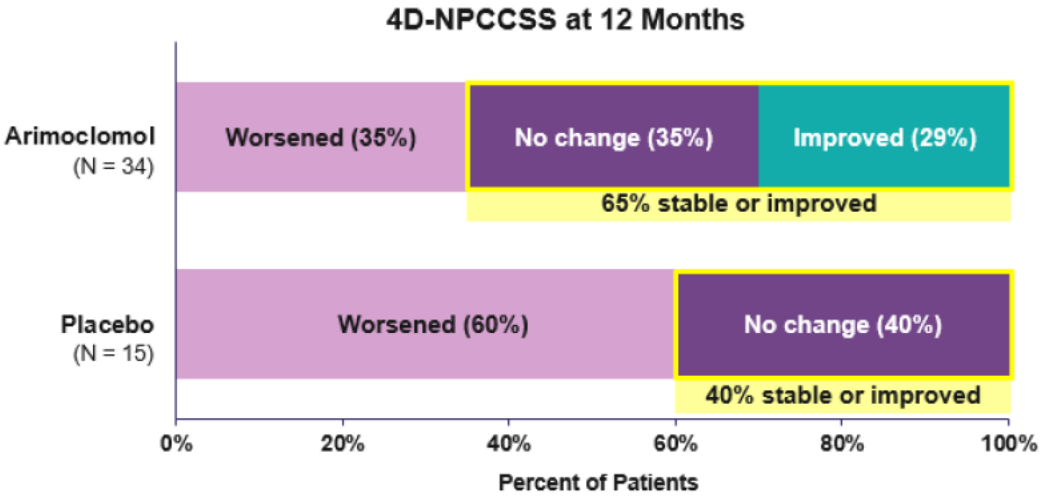
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; CI = confidence interval; FAS = Full Analysis Set.

1.5.3 Study 002 Patient-level Analysis

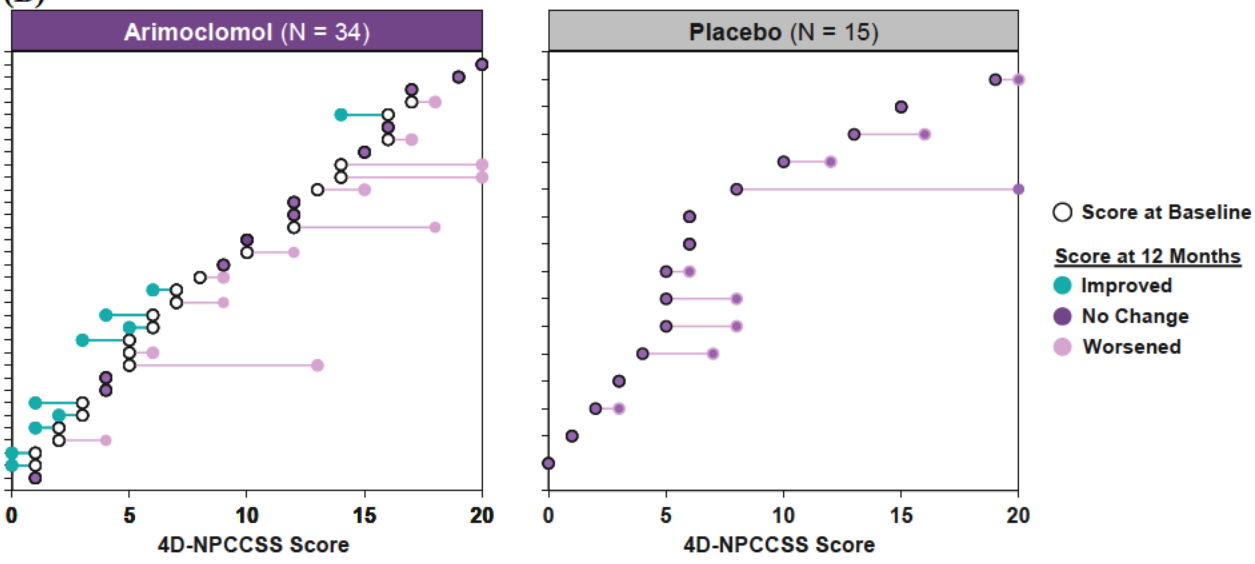
4D-NPCCSS was also analyzed at the individual patient level to evaluate differences in disease trajectory (Figure 3). Most patients who received arimoclomol (22/34 [64.7%]) saw their condition either stabilize or improve from baseline to the last visit. In contrast, the proportion of patients receiving placebo who stabilized was 40%; no patients improved, and 60% worsened.

Figure 3: Study 002: Patient-level Analysis of 4D-NPCCSS, Summary (A) and Per-patient (B) – Double-blind Phase (FAS)

(A)



(B)



Patient sorted by baseline score, followed by change from baseline. All three patients with double functional null mutation randomized to arimoclomol group.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; FAS = Full Analysis Set.

1.6 Confirmatory Evidence

The confirmatory evidence for arimoclomol consists of multiple sources representing independent types of scientific investigation, including clinical data, natural history data, MOA, and animal models of NPC. These data consistently align with, mutually reinforce, and fully support the treatment benefit observed in the randomized pivotal clinical trial.

1.6.1 Clinical Confirmatory Evidence of Efficacy

The clinical data consistently show slowing of disease progression in patients with NPC treated with arimoclomol relative to placebo or untreated patients.

Crossover from Placebo during Double-blind Phase of Study 002 to Arimoclomol during Open-label Extension (OLE) Phase

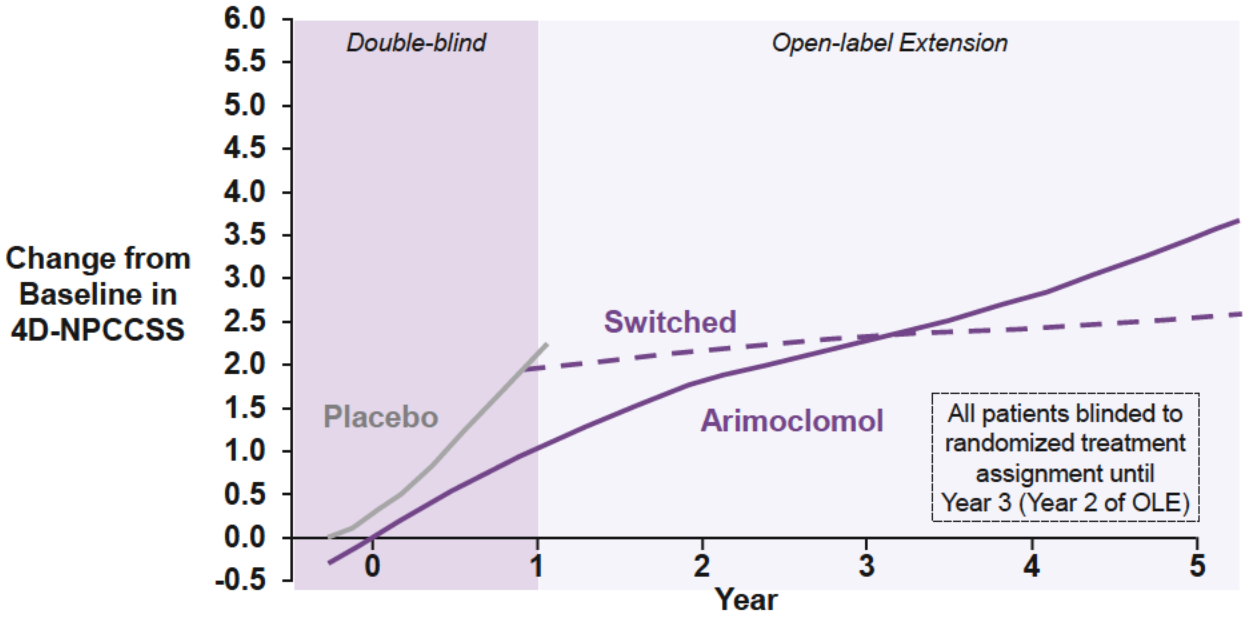
A total of 41 out of 42 patients who completed the double-blind phase of Study 002 continued into the OLE phase, during which all patients received arimoclomol for up to 4 additional years. Upon entering the OLE phase, patients and physicians were blinded to initial randomization assignment in Study 002, and they remained so through at least 2 years of participation in the OLE (Year 3 of Study 002). This design enabled continued investigation of arimoclomol effects because patients who initially received placebo could act as their own controls.

Among patients who switched from placebo to arimoclomol, the average rate of disease progression decreased from 1.9 points per year while receiving placebo during the double-blind phase to 0.3 points per year while receiving arimoclomol during the OLE phase. The decrease in progression rate in placebo patients is visualized in a LOESS plot of change in 4D-NPCCSS score from DB baseline vs actual treatment duration (Figure 4, solid gray vs dashed purple lines; Section 7.1.3.1).

Moreover, the average rate of progression among patients who received arimoclomol throughout both phases of Study 002 was relatively constant (0.82 points per year) through approximately 5 years of available data and did not change significantly between the double-blind (0.71 points per year) and OLE phase (0.93 points per year) (Figure 4, solid purple line; Section 7.1.3.1). A similar benefit of disease stabilization was also observed in patients enrolled in the Expanded Access Program (EAP; Section 7.1.4).

Given the progressive nature of NPC, such considerable and consistent change is unlikely due to chance, but rather indicates a treatment effect of arimoclomol and further supports the findings from the controlled, double-blind phase of the pivotal study.

Figure 4: Study 002: LOESS Plot of Change from Baseline in 4D-NPCCSS over Time during the Double-blind and Open-label Extension Phases (FAS plus Extension Set)



Arimoclomol	34	27	22	21	20	16
Placebo/Arimoclomol	15	15	12	12	11	9

Note: All patients blinded to randomized treatment assignment until Year 3 (Year 2 of OLE).
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; OLE = open-label extension.

Comparisons of Annual Rates of Change with Placebo/No Treatment vs Arimoclomol

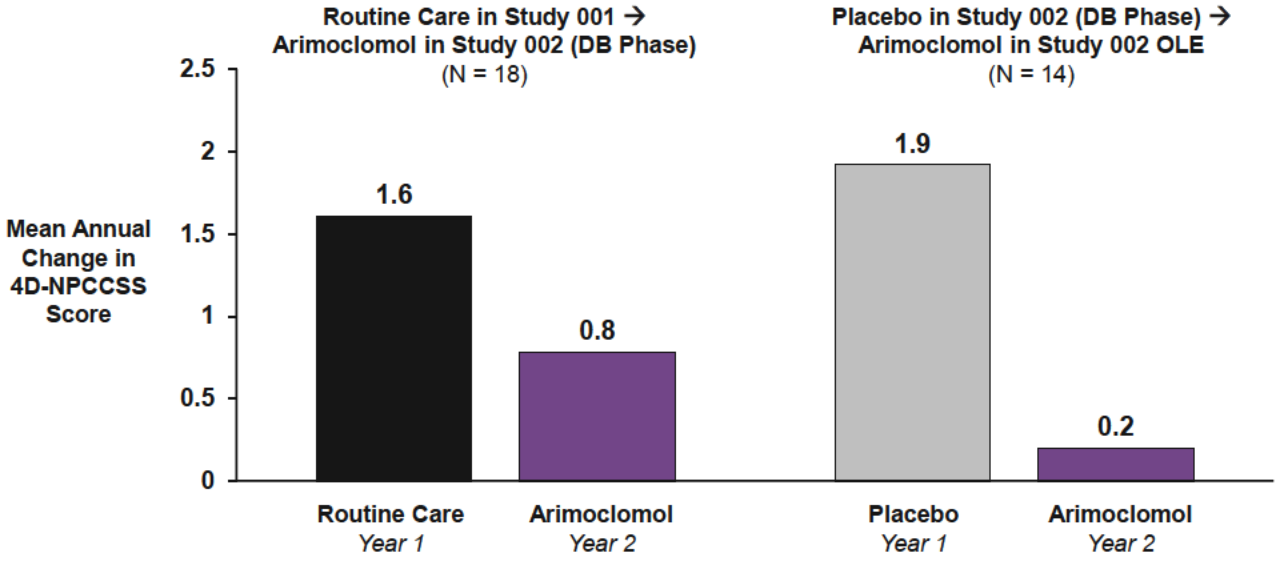
With data from Study 001, the double-blind period of Study 002, and the OLE of Study 002, two relevant intrapatient comparisons of the annual rates of change in disease progression can be evaluated with the 4D-NPCCSS as patients begin treatment with arimoclomol (Figure 5).

In both crossover comparisons, patients demonstrated a slower rate of disease progression during 1 year treatment with arimoclomol (either double-blind or OLE) compared to the preceding year on either routine care only or routine care plus placebo.

- 18 patients who participated in Study 001 (all of whom received routine care/observation only) in Year 1 progressed by 1.6 points but only by 0.8 points when receiving arimoclomol during the double-blind phase of Study 002 in Year 2 (N=18) (Figure 5; Section 7.1.3.2).
- 14 patients who received placebo in the double-blind phase of Study 002 in Year 1 progressed by 1.9 points but only by 0.2 points when receiving arimoclomol during the OLE phase of Study 002 in Year 2 (Section 7.1.3.1).

These results are comparable with the mean changes in 4D-NPCCSS score from baseline in the arimoclomol (0.71 points) and placebo (1.9 points) groups during the 1-year randomized double-blind phase of Study 002 (Sections 1.5.2 and 6.8.4.1).

Figure 5: Summary of Disease Progression Rates for Treated vs Untreated across Clinical Development Program



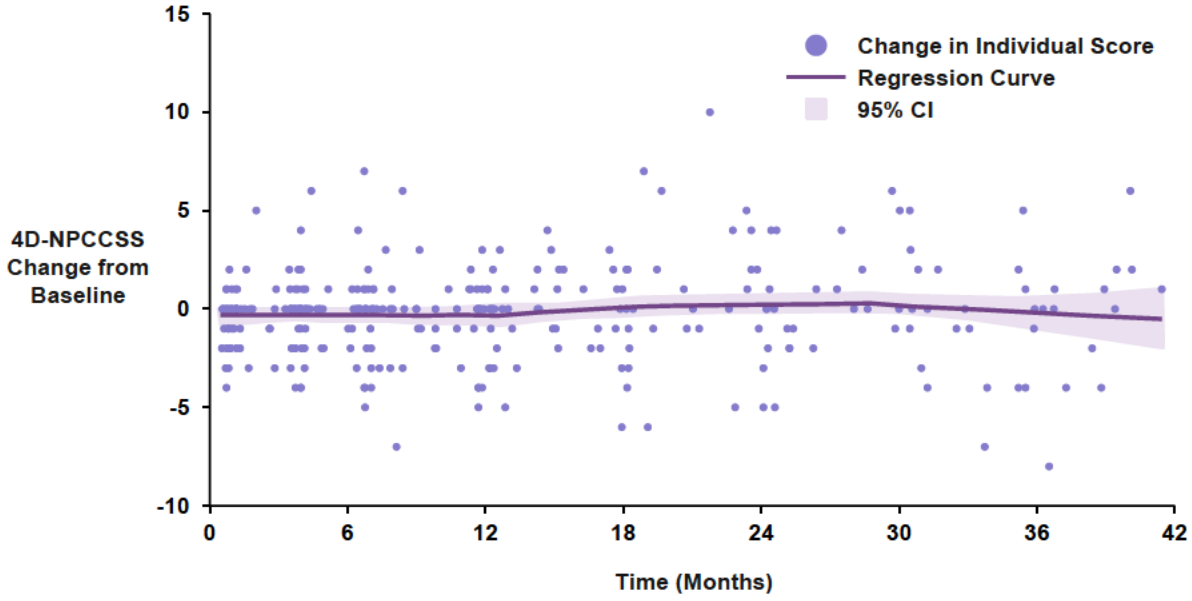
Note: Higher values indicate faster disease progression.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; DB = double-blind; OLE = open-label extension.

Expanded Access Program

Beginning in 2020, patients with NPC who did not participate in Study 002 were eligible to receive arimoclomol through an Expanded access Program (EAP). As of 1 February 2024, a total of 206 patients have received ≥ 1 dose of arimoclomol in the EAP, including 93 from the US.

EAP data indicate that the participants who received arimoclomol on average were stable for up to approximately 3.5 years with a slower disease progression as compared to untreated patients from Studies 001 (observational) and 002 (placebo) (Figure 6; Section 7.1.4).

Figure 6: LOESS Plot of 4D-NPCCSS Change from Baseline through 42 Months in Expanded Access Program



CI = confidence interval; 4D-NPCCSS = 4-domain Niemann-Pick, type C clinical severity scale with the updated swallow domain; LOESS = locally estimated scatterplot smoothing.
Note: Patients with only baseline score or patients with no baseline score (i.e., no score prior to treatment start) were excluded. The graph shows data starting with the first assessment after treatment start up to 42 months of follow-up. The regression line is based on actual study day (in months) for each patient.

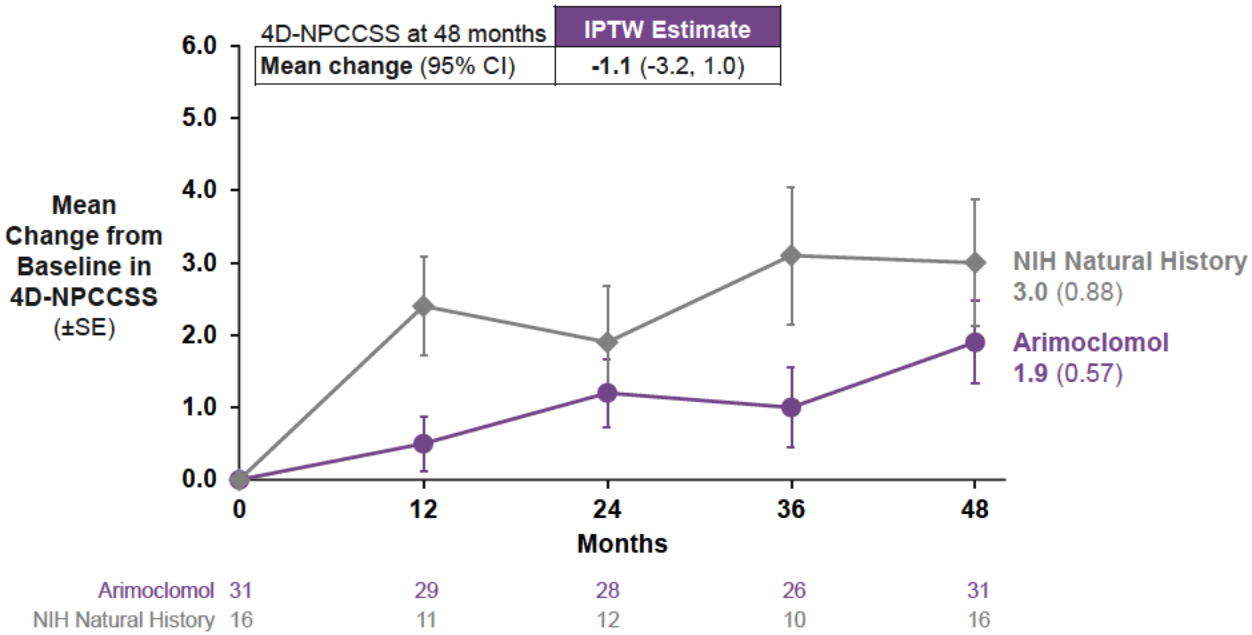
1.6.2 Natural History Confirmatory Evidence of Efficacy

During review of the Sponsor's resubmitted NDA, the FDA requested an analysis comparing patients treated with arimoclomol in the OLE phase of Study 002 with matched external comparators from the NIH natural history cohort study who had 4 years of follow-up data. Inverse probability of treatment weighting (IPTW) and a more conventional matching process were used to compare long-term outcomes between the two non-randomized groups on several factors: baseline age, sex, baseline miglustat use, age of disease onset, and baseline score.

Patients ≥ 4 years of age at baseline progressed more slowly when treated with arimoclomol for 4 years in the OLE phase of Study 002 (N=31) compared to controls from the NIH natural history cohort (N=16), as measured by 4D-NPCCSS scores (SE): 1.9 (0.57) vs 3.0 (0.88) for

arimoclomol vs NIH natural history cohort, respectively (Figure 7). Notably, during all 4 years of the Study 002 OLE phase the mean 4D-NPCCSS score increased by < 1 point per year, while scores in the NIH control cohort increased by > 1 point per year during years one and three. (See Section 7.1.3.3 for details on scoring for these cohorts.)

Figure 7: Mean Change from Baseline in 4D-NPCCSS in Patients Treated with Arimoclomol during the Open-label Extension Phase vs Matched NIH Natural History Patients



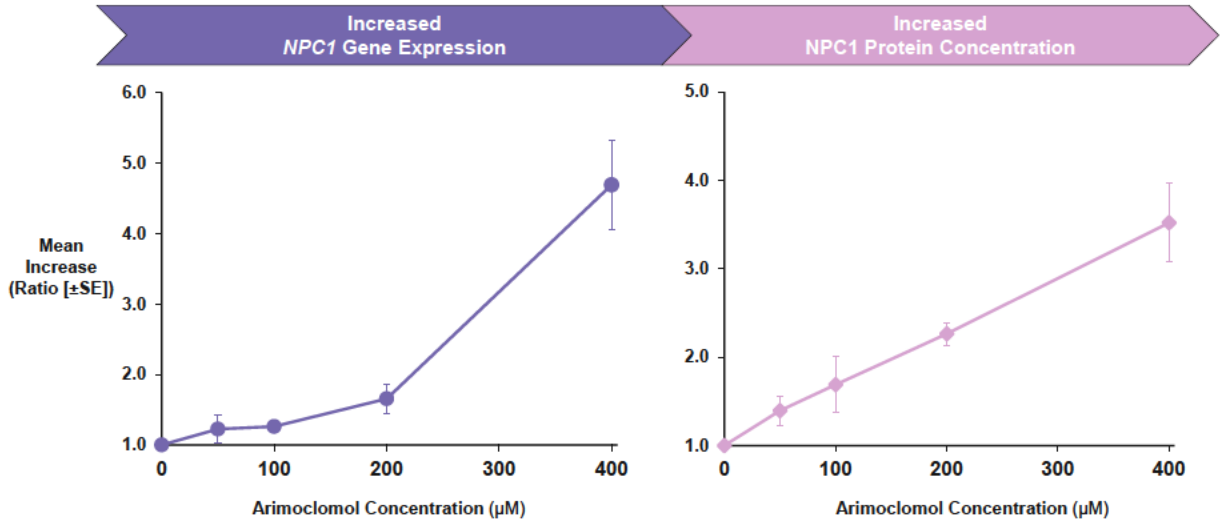
Note: the 4D-NPCCSS endpoint of both the NIH Natural History and the arimoclomol patient groups includes the original swallow domain.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; IPTW = inverse probability of treatment weighting; NIH = National Institutes of Health.

1.6.3 In Vitro Data Supporting Arimoclomol's Mechanism of Action

In vitro studies show that arimoclomol increases activation of the transcription factors EB (TFEB) and E3 (TFE3) by promoting their translocation into the nucleus. Once in the nucleus, arimoclomol enhances binding of TFE3/TFEB to coordinated lysosomal expression and regulation (CLEAR) motifs in the promoter regions of lysosomal genes. Since TFEB and TFE3 are master regulators of the CLEAR genes, which encode a multitude of proteins involved in various lysosomal and autophagosomal functions — including but not limited to NPC1 protein — arimoclomol can provide treatment effects through NPC1-dependent and NPC1-independent pathways.

Along the NPC1 biosynthesis and transport pathway, arimoclomol upregulates *NPC1* gene expression and thereby increases NPC1 protein concentrations. The impact of arimoclomol on gene expression and protein concentration was evaluated using in vitro NPC cell lines. Arimoclomol was associated with a dose-dependent upregulation of *NPC1* gene expression, which led to a substantial increase in NPC1 protein concentrations (Figure 8; Section 7.2.1.3).

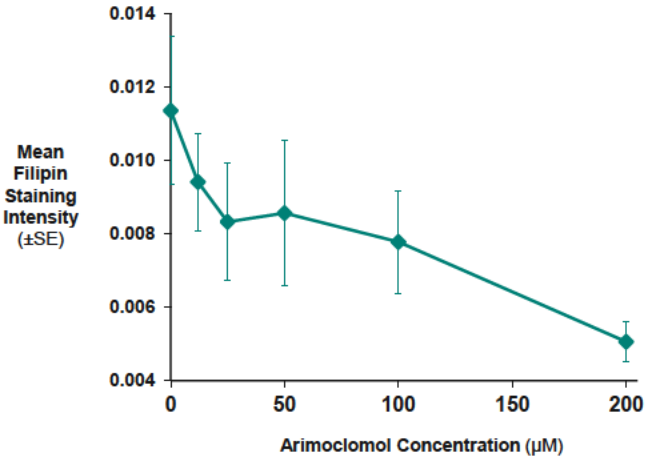
Figure 8: *NPC1* Gene and NPC1 Protein Level Expression in Fibroblasts from NPC Patients with Increasing Concentrations of Arimoclomol



NPC1 = Niemann-Pick disease, type C intracellular cholesterol transporter 1.

Importantly, data also showed that arimoclomol increased levels of folded and mature NPC1 mutant protein and not just overall cellular levels of NPC1 protein. Depending on the specific genotype and the functionality of the resulting mutant protein, this greater availability of trafficking competent NPC1 protein that can reach the late endosomal/lysosomal membranes results in various degrees of improved clearance of unesterified cholesterol. This outcome was demonstrated by the reduction of unesterified cholesterol in NPC patient fibroblasts treated with arimoclomol (Figure 9; Section 7.2.1.4).

Figure 9: Reductions in Unesterified Cholesterol in Fibroblasts from NPC Patients with Increasing Concentrations of Arimoclomol



NPC1 = Niemann-Pick disease, type C intracellular cholesterol transporter 1.

The MOA of arimoclomol is described in more detail in Section 3.3.1, and the confirmatory evidence from in vitro studies is presented in detail in Section 7.1.

1.6.4 Animal Models

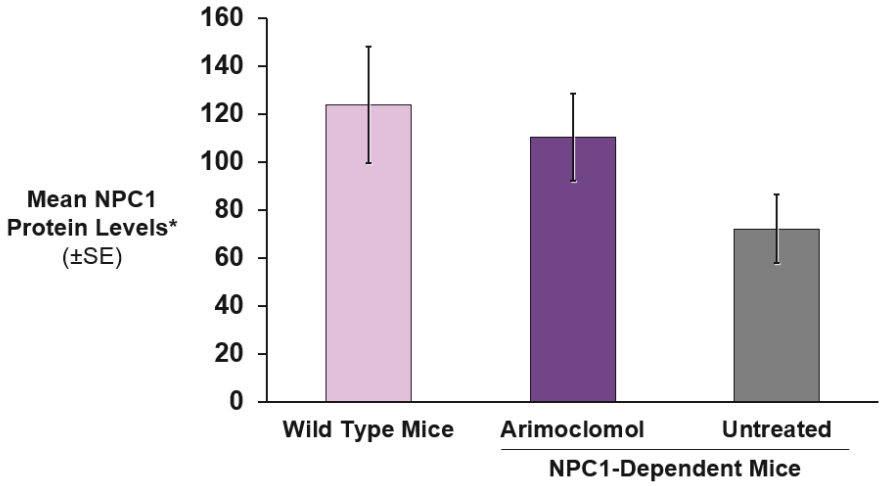
Studies conducted in two mouse models of NPC confirmed the mechanistic effects identified during the in vitro studies, further characterizing arimoclomol's beneficial effects. The mouse models used were:

- *Npc1*$^{-/-}$ knockout mice have double functional null mutations and are a model for severe disease with no functional NPC1 protein synthesis (referred to herein as "NPC1-independent" model).
- *Npc1*^{nmf164} mice have a point mutation and are a model for a milder form of disease with diminished levels of NPC1 protein that retained some function (referred to herein as "NPC1-dependent" model).

1.6.4.1 Increased Levels of Mature NPC1 Protein in NPC Mice

When treated with arimoclomol, NPC-dependent (*Npc1*^{nmf164}) mice demonstrated levels of mature and properly folded NPC1 protein that were comparable to levels measured in healthy, wild-type mice (Figure 10). In addition, the mean concentration of NPC1 protein in treated mice was approximately 50% greater than that found in untreated mice.

Figure 10: Concentrations of Mature Isoform 1 of NPC1 Protein in Brains of Wild-type, Untreated, and Arimoclomol-treated NPC-dependent (*Npc1*^{nmf164}) Mouse



* NPC1 protein levels (isoform 1: >250 kDa and isoform 2: ~150 kDa) are normalized to tubulin.
Note: NPC1-dependent mice (*Npc1*^{nmf164}) have a D1005G point mutation.
NPC1 = NPC intracellular cholesterol transporter 1.

1.6.4.2 Effect on Functional and Survival Endpoints in NPC Mice

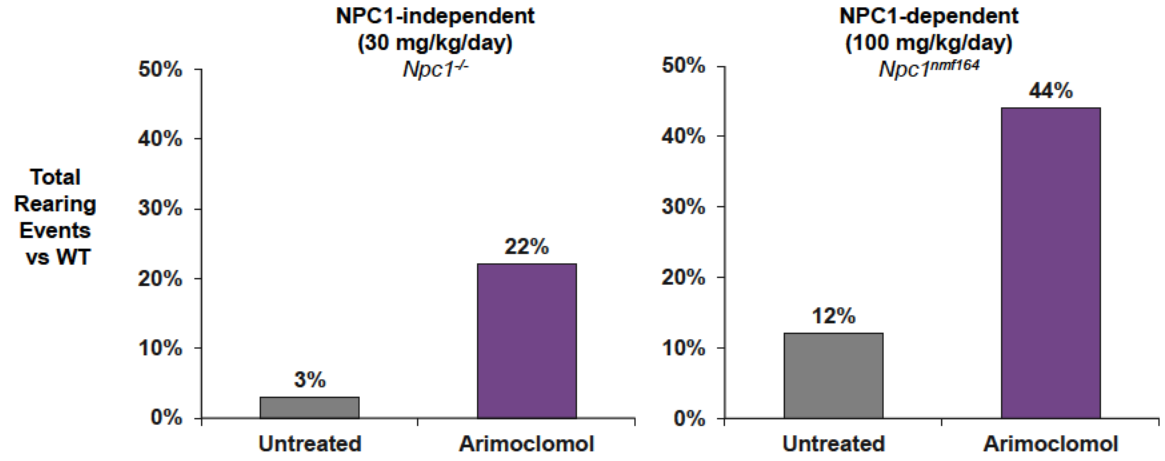
Rearing Activity

The consequence of CLEAR network upregulation and increased NPC1 protein was also seen in the behaviors observed in the two mouse models of NPC (NPC1-independent [*Npc1*$^{-/-}$] and NPC1-dependent [*Npc1*^{nmf164}]). Rearing is a key behavior for mice as they explore their environment, interact with each other, and ultimately find food and water. Rearing activity in mice not only informs on the ability to stand on the hind legs but is also an indicator of exploratory activity and emotional responsiveness (Alves et al., 2012; Chen et al., 2023).

Moreover, rearing is an important indicator of neuronal health, particularly in the cerebellum, hippocampus, and midbrain of the mouse (Rochefort et al., 2011; Alves et al., 2012; Krook-Magnuson et al., 2014; Onuki et al., 2015). These are the same brain regions that are affected in humans with NPC resulting in deterioration of fine motor movements and swallowing/chewing function among other clinical symptoms.

In vivo studies with NPC mice show increased rearing compared to untreated animals, and this effect was observed in both NPC1-independent and NPC1-dependent mouse models (Figure 11).

Figure 11: In Vivo Mouse Studies: Rearing Behaviors with Arimoclomol Treatment

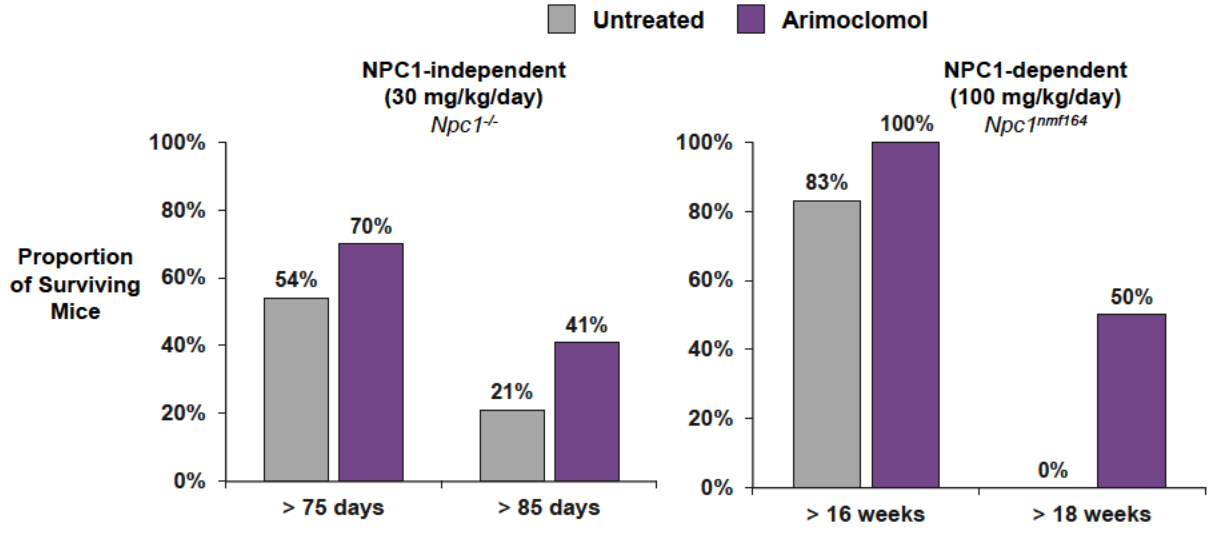


NPC1 = Niemann-Pick disease, type C intracellular cholesterol transporter 1; WT = wild type.

Survival

The mouse models also show that the mechanistic effects characterized through in vitro studies produce beneficial survival effects in vivo (Figure 12). A favorable trend was observed with arimoclomol treatment vs untreated animals in both NPC1-independent and NPC1-dependent mice. Notably, in the NPC1-dependent mice, only arimoclomol-treated animals lived > 18 weeks.

Figure 12: In Vivo Mouse Studies: Proportion of Survival with Arimoclomol Treatment



NPC1 = Niemann-Pick disease, type C intracellular cholesterol transporter 1.

1.7 Clinical Safety

The totality of safety data demonstrates that arimoclomol has a safety profile that is acceptable and well-tolerated and does not add to the high patient burden of NPC. In total, 874 individuals have received arimoclomol: 668 individuals in clinical studies across all indications and 206 individuals in the EAP. The primary safety data for patients with NPC treated with arimoclomol is from Study 002, which includes 50 patients in the double-blind phase and 41 patients in the OLE for up to 4 years (Table 2). Arimoclomol's total safety profile has proven consistent and acceptable in 668 healthy subjects and patients across 4 indications receiving at least one dose of arimoclomol in 18 clinical studies (5 with OLE phase). (A summary of common adverse events across indications is presented in Table 40; Appendix 11.2.)

Table 2: Summary of Safety in Study 002 (Double-blind and OLE Phases)

	Double-blind Phase		Open-label Extension
Adverse Event, n (%):	**Arimoclomol (N=34)**	**Placebo (N=16)**	**Arimoclomol (N=41)**
Any AE	30 (88.2)	12 (75.0)	38 (92.7)
Serious AE	5 (14.7)	5 (31.3)	15 (36.6)
AE leading to discontinuation	3 (8.8)	0	4 (9.8)
AEs with fatal outcome	1 (2.9)	0	2 (4.9)

AE = adverse event.

1.7.1 Treatment Exposure

Across all completed clinical studies, a total of 668 patients have received arimoclomol for a combined 708.1 patient-years of exposure (Table 3).

In Study 002, thirty-four (34) patients with NPC were exposed to arimoclomol at the recommended body weight-based dose during the 1-year double-blind phase, and 41 total patients received arimoclomol during the 4-year OLE phase (Table 32; Section 8.1). Patients in both phases received the recommended body weight-adjusted t.i.d. dosing of arimoclomol. (See Table 6 for recommended dose.)

Table 3: Summary of Arimoclomol Exposure: All Completed Studies

Exposure:	**Arimoclomol (N=668)**	**Placebo (N=264)**
Total days	258,465	93,172
Mean (SD)	386.9 (424.6)	352.9 (227.5)
Median (min–max)	248.0 (1–1,923)	375.0 (1–631)
Duration of exposure (weeks), n (%)		
≥ 4 Weeks	553 (82.8)	235 (89.0)
≥ 26 Weeks	387 (57.9)	175 (66.3)
≥ 52 Weeks (≥ 1 year)	231 (34.6)	142 (53.8)
≥ 104 Weeks (≥ 2 years)	140 (21.0)	0

SD = standard deviation.
Note: Includes all participants receiving at least 1 dose of arimoclomol.

1.7.2 Overall Safety of Study 002: Double-blind Phase

In Study 002, adverse events (AEs) were reported at comparable proportions in both treatment groups: 88.2% vs 75.0% for arimoclomol vs placebo, respectively (Table 4). Most events were mild-to-moderate in severity in both treatment groups. Patients taking placebo reported more frequent serious AEs (SAEs): 14.7% vs 31.3% for arimoclomol vs placebo, respectively. Only 2 SAEs occurred in more than 1 patient, urticaria in the arimoclomol group and pneumonia in the placebo group (Table 34; Section 8.3.2).

Three patients (8.8%) in the arimoclomol group reported AEs that led to discontinuation. The AEs leading to discontinuation were urticaria/angioedema (2 events), and blood creatinine increased (1 event). These AEs were moderate in severity, and all patients recovered without sequelae.

One death due to an AE occurred in the arimoclomol group during the double-blind phase and was adjudicated as not related to arimoclomol. (See additional details in Section 8.3.4 and narrative in Appendix 11.1.1).

Table 4: Study 002: Summary of Adverse Events (Double-blind Phase)

Adverse Event, n (%):	Arimoclomol (N=34)	Placebo (N=16)
Any AE	30 (88.2)	12 (75.0)
Mild	27 (79.4)	12 (75.0)
Moderate	26 (76.5)	9 (56.3)
Severe	4 (11.8)	3 (18.8)
Serious AE	5 (14.7)	5 (31.3)
AE leading to treatment discontinuation	3 (8.8)	0
AE with fatal outcome	1 (2.9)	0

AE = adverse event.

1.7.3 Overall Safety of Study 002: Open-label Extension Phase

Of the 42 patients who completed the double-blind phase, 41 patients enrolled in the OLE phase, during which all patients received arimoclomol. During the OLE, nearly all patients (38/41 [92.7%]) received arimoclomol for ≥ 1 year, and 34/41 (82.9%) received arimoclomol for ≥ 2.5 years.

Importantly, the safety profile reported during the 4-year OLE phase of Study 002 (Table 5) remained generally consistent with the 1-year double-blind phase (Table 4). Two patients died during the OLE while on arimoclomol. Neither death was considered related to arimoclomol. (Narratives provided in Appendix 11.1.2).

Table 5: Study 002: Summary of Adverse Events (Open-label Phase)

Adverse Event, n (%):	Arimoclomol (N=41)
Any AE	38 (92.7)
Severe AE	15 (36.6)
Serious AE	15 (36.6)
AE leading to discontinuation of treatment	4 (9.8)
AE with fatal outcome	2 (4.9)

AE = adverse event.

1.8 Benefit-Risk Summary

The present NDA resubmission aligns with regulatory principles outlined for rare diseases in the new FDA draft guidance document *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (FDA, 2023). The guidance specifies that substantial evidence of effectiveness can come from one adequate and well-controlled clinical study plus confirmatory evidence. Confirmatory evidence may be based on multiple sources of information, including but not limited to clinical studies, animal data, and mechanistic information.

Evidence of Effectiveness

The NDA resubmission meets the regulatory requirements for demonstrating substantial evidence of effectiveness in the following ways:

- **One adequate and well-controlled randomized trial:** Study 002 showed a clinically meaningful and statistically significant result for arimoclomol on the FDA-recommended primary endpoint of 4D-NPCCSS with the while-on-treatment estimand. Findings were supported by a series of sensitivity analyses, and the treatment effect exceeded the MCID.
- **Confirmatory evidence:** Confirmatory evidence across multiple sources supports the favorable clinical outcome from Study 002.
    - **Clinical:** Patients who switched from placebo in the double-blind phase of Study 002 to arimoclomol in the OLE phase reported a slowing of disease progression, which was sustained for up to 4 years of open-label treatment. Moreover, patients randomized to arimoclomol in the double-blind phase maintained a similar average progression rate through both study phases for up to 5 years of arimoclomol treatment. When arimoclomol patients were matched with the NIH natural history cohort, arimoclomol treatment resulted in slower disease progression over 4 years.
    - **In vitro**: Arimoclomol's MOA benefits patients through multiple pathways, upregulating both the synthesis of NPC1 protein and the CLEAR gene network, all of which are critical for lysosomal function and resulted in improved cholesterol clearance from lysosomes.
    - **In vivo**: NPC mouse models confirm arimoclomol's mechanism, demonstrating increased brain concentrations of mature NPC1 protein, improved rearing behaviors, and most importantly, increased survival.

Overall, arimoclomol showed meaningful benefits across all studies and various analyses. Importantly, all experimental results confirmed findings from others without contradiction providing additional confidence and support of the effectiveness of arimoclomol.

Acceptable Safety Profile

With an extensive safety database that includes 708.1 patient-years of arimoclomol exposure in 874 individuals, including 668 healthy subjects and patients across four indications in 18 clinical studies (5 with OLE phase), and 206 patients in the EAP, arimoclomol is consistently well-tolerated with an acceptable safety profile. This finding includes patients with NPC, who have up to 5 years of follow-up in Study 002. Importantly, treatment with arimoclomol does not add to the burden of disease for patients with NPC.

Favorable Benefit-Risk with Substantial Evidence of Effectiveness

At present, there is no cure and no FDA-approved therapy for NPC. Arimoclomol offers patients with NPC a well-tolerated and easy-to-administer therapy that significantly slows disease progression and leads to clinically meaningful benefits for patients. The totality of data provides substantial evidence of effectiveness and a positive benefit-risk profile for arimoclomol, supporting its approval for the treatment of NPC.

2. Unmet Medical Need

Summary

- NPC is an ultra-rare, severely debilitating, and fatal neurodegenerative disease, characterized by a relentless loss of function that usually leads to death before adulthood.
- Approximately 600–900 US residents have NPC, which occurs in about 1:100,000 births.
- NPC manifests most commonly during childhood and adolescence, with earlier onset of neurological symptoms predictive of more rapid disease progression.
  - Age of onset varies from neonatal, rapidly progressive disorder to an adult onset, slowly progressing disease.
- The hallmark clinical complication is progressive neurological damage in the brain that culminates with severe encephalopathy and fatal dementia.
- NPC etiology originates with loss-of-function variants in the *NPC1* and/or *NPC2* genes, which lead to lysosomal dysregulation and buildup of lysosomal cholesterol.
- Symptoms are caused by accumulation of lysosomal cholesterol, which results in cellular dysfunction and death, primarily in the liver, spleen, lungs, and brain.
- Eventually, NPC leads to complete dependency on family and caregivers and has a substantial impact on all aspects of the life of the patients and their families.
- There are no approved disease-modifying therapies for NPC in the US.

2.1 Overview of Niemann-Pick Disease Type C

2.1.1 Epidemiology

NPC is an ultra-rare disease that affects an estimated 600–900 people in the entire United States, with an incidence rate of approximately 1 in 100,000 births (Burton, 2021; Geberhiwot, 2018). NPC manifests most commonly during childhood and adolescence but can present at any stage of life with highly diverse symptomatology and with variable speed and patterns of progression, ranging from a neonatal, rapidly progressive disease to an adult-onset, slowly progressing, neurodegenerative disease. NPC can be categorized by age of neurological symptoms: early infantile (onset before age 2), late infantile (onset between ages 2 and 6), juvenile (onset between ages 6 and 15), and adult-onset (after age 15). The disease progression largely correlates with the age of onset of the neurologic symptoms. Earlier age of onset for neurological signs and symptoms predicts more rapid disease progression. However, no single symptom can predict the disease progression rate, and there are no established biomarkers to predict for progression or severity (Vanier, 2010; Yanjanin et al., 2010).

2.1.2 Disease Pathology

NPC is a genetic disease, inherited in an autosomal recessive pattern, where both parents contribute a mutated *NPC1* or *NPC2* gene to their child. In 95% of cases, NPC is caused by mutations in the *NPC1* gene (Vanier, 2010; Geberhiwot et al., 2018). Double functional null NPC1 genotype predicts an early infantile age of onset and severe NPC. *NPC1* and *NPC2* genes encode lysosomal proteins that are essential in intracellular transport and metabolism of cholesterol and other lipids. The dysfunction of either of these NPC genes results in a reduced

amount of properly folded and mature NPC1 protein. The consequence is lysosomal dysfunction with accumulation of lipids resulting in a negative impact on downstream pathways. For example, lysosomal sphingolipid degradation becomes impaired leading to accumulation of several complex sphingolipids in various tissues including the brain and liver (Vanier and Latour, 2015; Breiden and Sandhoff, 2020). This lipid accumulation is cytotoxic and causes neurodegeneration and peripheral organ dysfunction (Lloyd-Evans and Platt, 2010; Platt, 2018). Visceral, systemic forms of the disease present first, including cholestasis and an enlarged spleen. NPC is characterized by a variety of heterogenous disabling symptoms including epilepsy and difficulties with basic functions such as walking, motor coordination, swallowing, speaking, concentrating, and remembering, that can require frequent hospitalization (Vanier, 2010; Stampfer et al., 2013; Wraith et al., 2014; Patterson et al., 2017).

2.1.3 Diagnosis

The diagnosis of NPC often requires a multidisciplinary approach and includes clinical assessment, biomarker testing, and genetic analyses.

Children with NPC may initially present with delays in reaching normal developmental milestones before manifesting cognitive decline and dementia. Neurological signs and symptoms include cerebellar ataxia, dysarthria, dysphagia, tremor, epilepsy (both partial and generalized), vertical supranuclear palsy (up gaze palsy, down gaze palsy, saccadic palsy or paralysis), sleep inversion, gelastic cataplexy, dystonia, spasticity, hypotonia, ptosis, microcephaly, psychosis, progressive dementia, progressive hearing loss, bipolar disorder, and major and psychotic depression that can include hallucinations.

In cases where the disease has been confirmed in one child, the sibling can be diagnosed with NPC by genetic testing before the onset of any visible signs or symptoms. However, even monozygotic twins with identical mutations can present extreme phenotypic heterogeneity of NPC resulting in, for example, severe neurological and psychiatric symptoms in one sibling and no to very mild neurological symptoms in the twin (Benussi et al., 2015). The reasons for this large variability in symptoms — even in identical genotypes — are likely due to epigenetic differences and post-zygotic mutagenesis.

The high variability of most signs and symptoms of NPC, combined with little or no experience with the disease among clinicians, leads to substantial diagnostic delays, misdiagnoses, and delayed intervention.

2.1.4 Prognosis/Survival

The extent of neurological involvement defines disease severity in most patients, and disease progression largely correlates with the age of onset of neurologic symptoms. The disease-defining neurodegeneration is typically preceded by systemic signs of liver, spleen, and lung involvement. This is particularly true for patients with onset during infancy and childhood. Neurological signs and symptoms include ambulation and walking difficulties, cognitive impairment, swallowing difficulties, vertical supranuclear gaze palsy, seizures, and cataplexy.

Disease progression imposes a substantial and progressive burden on patients, their families, and their caregivers, culminating in severe encephalopathy that causes complete loss of motor control, total ophthalmalgia, uncontrolled persistent seizures, and premature death. The median life expectancy for patients with NPC is 13 years, which has changed very little over the last 20 years (Bianconi et al., 2019).

2.2 Current Treatment Options

2.2.1 Standard of Care

There are no FDA-approved pharmaceutical therapies for the treatment of NPC. All pharmacotherapies are either symptom-based or used off-label.

Disease management employs a multidisciplinary team, ideally based in a specialist center, that closely liaises with community care providers. The mainstay of pharmacological therapy is symptom management with anti-seizure medications; antibiotics; anti-spastic therapies, such as onabotulinumtoxinA (Botox) and baclofen; and anti-psychotic medication (Alobaidy, 2015; Geberhiwot et al., 2018).

Non-pharmacological interventions include physiotherapy, speech and oral therapy, and percutaneous endoscopic gastrostomy tube when oral feeding cannot sustain stabile nutrition. These interventions are widely used in patients with neurological impairment (Sheikh and Vissing, 2019).

In the absence of any FDA-approved therapies, miglustat is frequently used off-label in the US, where it is approved only for the treatment of adults with mild/moderate type 1 Gaucher disease (Hastings et al., 2019). Miglustat reversibly inhibits glucosylceramide synthase and thus may work as a partial substrate reduction therapy in NPC.

2.3 Unmet Medical Need Conclusions

NPC is a very heterogeneous, relentlessly progressive, neurodegenerative disease that ultimately results in early death. Non-specific symptoms present in irregular patterns that vary by person – with some progressing rapidly in a 12-month period and some progressing more slowly. Patients endure a progressive and substantial decline in both function and quality of life. This impact on patients and their caregivers cannot be understated given the nature of the disease, the burden of care, and the emotional toll on caregivers as the patients afflicted with the most severe and progressive manifestations of the disease are often young children.

As no FDA-approved pharmaceutical therapies are available for the treatment of NPC, there is a high unmet medical need for effective and safe pharmacological treatments that can delay the progression of this severely debilitating and fatal disease.

3. Product Description

Summary

- Arimoclomol is a small molecule, orally bioavailable therapy with an MOA that targets the fundamentals of NPC etiology.
- Arimoclomol increases activation of TFEB and TFE3, resulting in upregulation of CLEAR genes, which encode proteins required for lysosomal function, including NPC1 and NPC2.
  - Increased CLEAR gene expression enables more NPC1 and NPC2 proteins to mature and migrate to the lysosomes where they transport cholesterol out of the cell.
  - Upregulation of CLEAR genes other than *NPC1* and *NPC2* can also promote lysosomal biogenesis and autophagy to improve overall cell health.
- Arimoclomol is administered as a capsule. For patients with swallowing difficulties the content of the capsules can be added to beverages/food or administered with water via a feeding tube.
- Arimoclomol does not affect genetic material and is not considered a gene therapy. Its effects are reversible upon discontinuation.

3.1 Proposed Indication

The proposed indication of arimoclomol is for the treatment of adult and pediatric patients (≥ 2 years) with NPC.

3.2 Recommended Dosing

Arimoclomol is taken 3 times a day at a weight-based dose (Table 6) with or without food. The dosages and body weight ranges were selected to provide similar exposure in patients of all ages that maximizes effectiveness while providing a sufficient safety margin. Capsules can be either swallowed whole or opened (sprinkle type) and added to beverages or food. The contents can also be added to water to allow administration via a feeding tube.

Table 6: Recommended Arimoclomol Dose by Body Weight Category

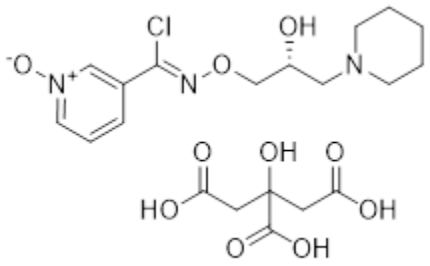
Patient Body Weight (kg):	Recommended Dose
8 to 15	47 mg t.i.d. (141 mg/day)
> 15 to 30	62 mg t.i.d. (186 mg/day)
> 30 to 55	93 mg t.i.d. (279 mg/day)
> 55	124 mg t.i.d. (372 mg/day)

t.i.d. = 3 times daily.

3.3 Product Overview

Arimoclomol citrate (N-[(2R,Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrate) is an orally bioavailable small molecule (Figure 13). Arimoclomol is not a gene therapy and does not alter the patient's genetics. Rather, it is a small molecule that upregulates expression of several genes in the CLEAR network, resulting in improved lysosomal function and slowing of disease progression.

Figure 13: Structure of Arimoclomol Citrate



3.3.1 Mechanism of Action

3.3.1.1 Role of NPC1 in Normal Lysosomal Function

Healthy lysosomal function requires a number of proteins regulated by TFEB and TFE3 to maintain homeostasis. The ratio of cytosolic and nuclear pools of these transcription factors determines the degree of their activation whereby translocation to the nucleus correlates with increased gene expression. Both transcription factors promote expression of genes responsible for lysosomal protein synthesis and other autophagy related functions (Figure 14, Panel A). Lysosomes are organelles responsible for removing waste materials from the cell. Genes activated by TFEB and TFE3 are collectively known as the CLEAR network of genes. In cells unaffected by NPC, normally assembled and maturated NPC protein migrates to the lysosomal membrane where they play a critical role in transporting cholesterol out of the lysosome. In healthy cells, this process supports elimination of waste (autophagy) to maintain healthy cellular function.

3.3.1.2 Pathophysiology of Niemann-Pick Disease

In patients with NPC missense mutations, the NPC1 protein typically has diminished quantity and functionality because mutations in the *NPC1* genes prevent most NPC1 protein from completing assembly and maturation in the endoplasmic reticulum (ER) and Golgi apparatus (Figure 14, Panel B). The degree of early degradation and residual protein function depends on the genotype. Nonetheless, a large portion of mutations including the most common I1061T variant remain functional but are subject to early degradation by quality control checks in the ER. As a result, only very small amounts of NPC1 protein are being incorporated into lysosomal membranes, leading to cholesterol accumulation and neuronal death (Gelsthorpe et al., 2008).

3.3.1.3 Mechanism of Action of Arimoclomol in the NPC Disease State

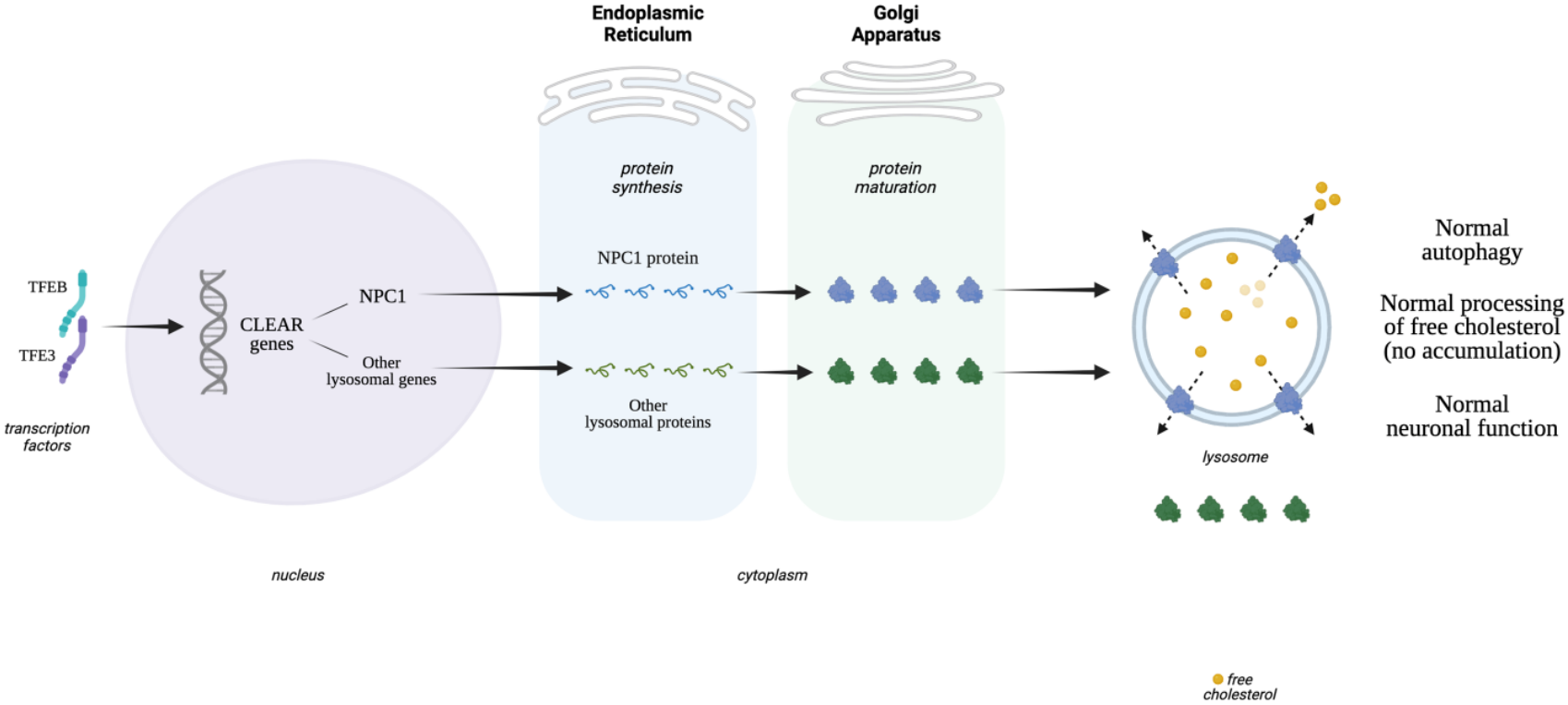
Arimoclomol targets NPC etiology by both NPC1-dependent and NPC1-independent pathways (Figure 14, Panel C).

- **NPC1-dependent pathway:** CLEAR gene upregulation increases production of the NPC1 protein. Though still mutated, overproducing the protein that typically has residual function if trafficked properly improves lysosomal function through increased export of cholesterol.
- **NPC1-independent pathway:** Arimoclomol upregulates expression of CLEAR genes, thereby rescuing impaired autophagy flux to improve overall cell health and lifespan.

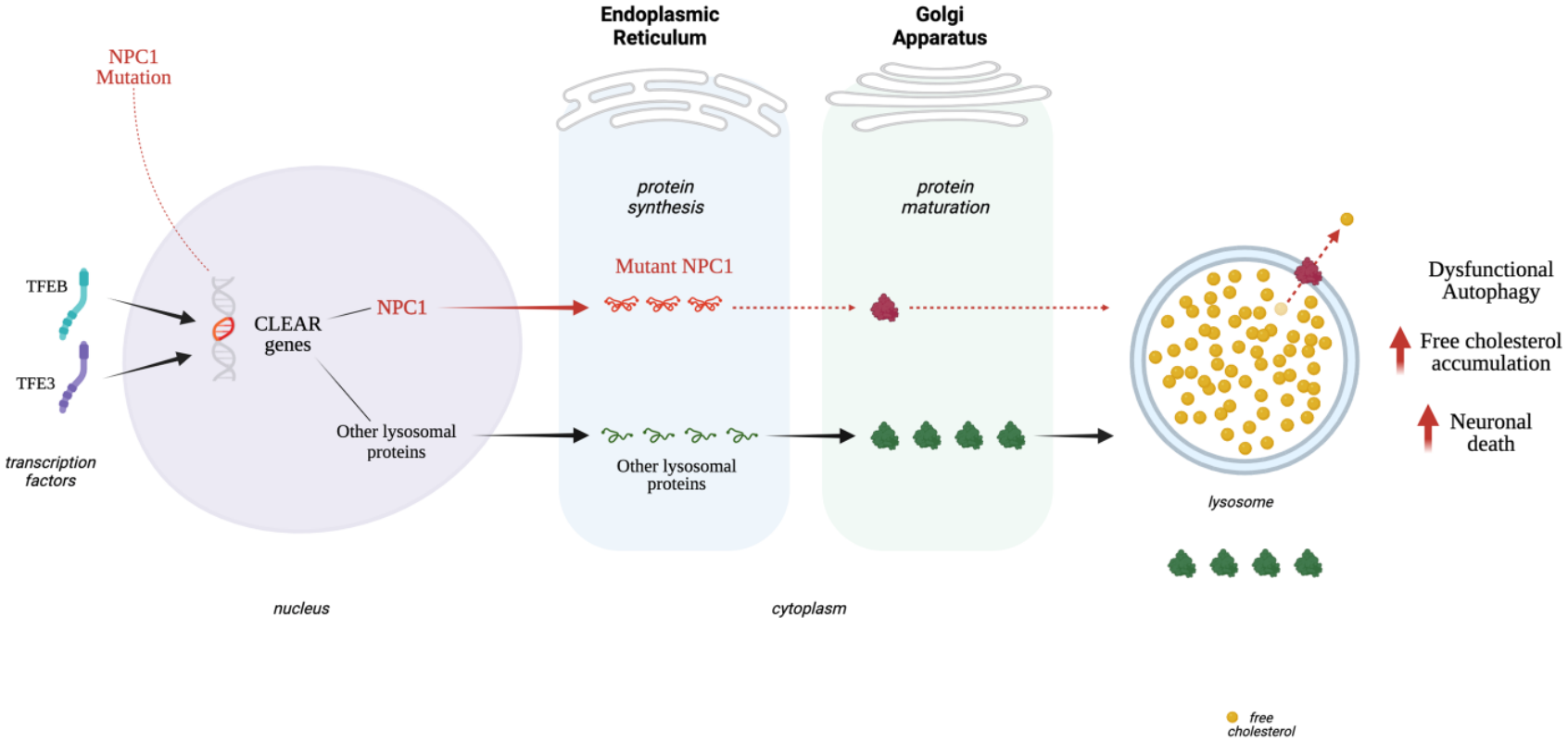
The in vitro data demonstrating the mechanistic pathway by which arimoclomol targets the fundamentals of NPC etiology is presented in Section 7.1.

Figure 14: Role of NPC1 in Normal Lysosomal Function (A), Untreated NPC Disease State (B), and Arimoclomol Mechanism of Action in NPC (C)

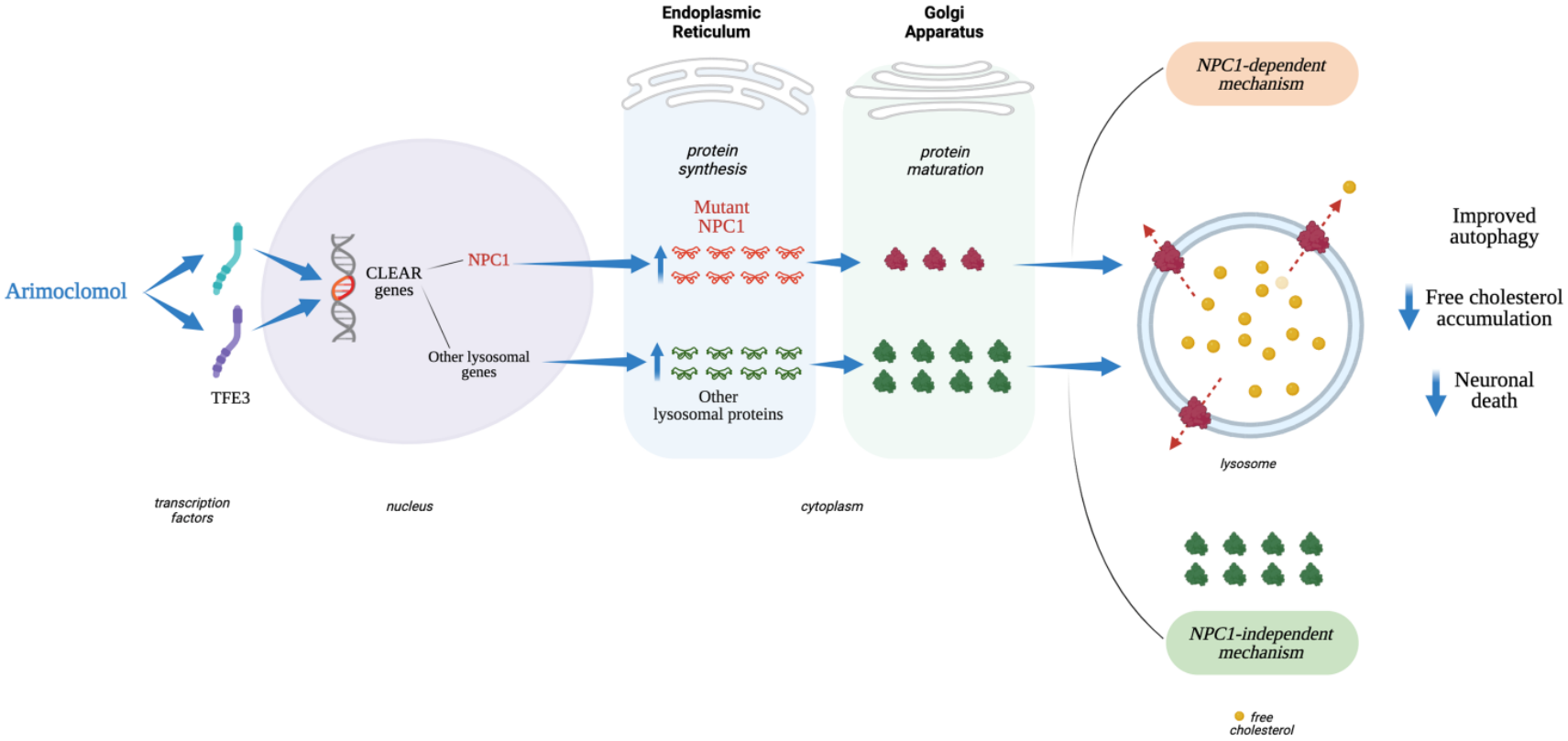
(A) Role of NPC1 in Normal Lysosomal Function



(B) Role of NPC1 in Untreated NPC Disease State



(C) Arimoclomol Mechanism of Action in NPC



CLEAR = Coordinated Lysosomal Expression and Regulation; NPC1 = Niemann-Pick disease, type C; TFE3 = transcription factor E3; TFEB = transcription factor EB.

4. Regulatory and Development History

Summary

- The clinical development program for arimoclomol treatment of NPC has been granted Orphan Drug Designation, Fast Track Designation, Breakthrough Therapy, and Rare Pediatric Disease Designation from the FDA.
- Following a CRL, Zevra implemented FDA's recommendations to strengthen the validity of the primary endpoint, perform new analyses of clinical data, and collect additional sources of confirmatory evidence.
- The primary safety and efficacy data are derived from Study 002, a Phase 2/3 randomized, placebo-controlled trial in patients with NPC, including a 12-month double-blind phase and a 4-year OLE phase.

4.1 Regulatory Milestones

The clinical development program for arimoclomol treatment of NPC is based on multiple interactions with health authorities and several meetings with the FDA. The Investigational New Drug (IND) Application for arimoclomol for the treatment of NPC was submitted on May 9, 2016. Orphan Designation, Fast Track Status, Breakthrough Therapy, and Rare Pediatric Disease Designation were also granted during development.

The original NDA 214927 for arimoclomol was submitted for rolling review in 3 parts from May to July 2020.

On June 17, 2021, the FDA issued a CRL. The letter outlined the deficiencies identified by the FDA and their recommendations to address these issues.

The key issues included in the CRL can be grouped into 3 main categories:

1. Validity and reliability of the abbreviated NPCCSS instrument.
2. Appropriate estimand for the primary efficacy analysis.
3. Robustness of confirmatory evidence.

A Type A end-of-review meeting was held under the NDA on October 13, 2021, to seek FDA guidance on how to address the CRL deficiencies. Alignment was reached to remove the cognition domain from the 5D-NPCCSS primary endpoint. In addition, the FDA recommended conducting a qualitative study of the swallow domain to address concerns raised in the CRL. As response to a post-meeting comment provided in the Type A meeting minutes, the Sponsor submitted draft documents for a qualitative study of the swallow domain of the NPCCSS.

On September 20, 2022, a Type B meeting was held to discuss the results of the completed Qualitative Study as well as additional evidence to support validity of the new 4D-NPCCSS endpoint with the updated swallow domain. Furthermore, the results of the primary efficacy analysis based on the while-on-treatment estimand, as recommended by the FDA, were presented. The FDA explained that no agreement could be reached on the topics of validity of the primary endpoint and substantial evidence of effectiveness without a discussion of confirmatory evidence. Consequently, the FDA recommended the Sponsor submit all available

nonclinical studies and request another meeting to discuss the results of those studies, which led to the meeting on August 10, 2023.

On August 10, 2023, a Type B meeting was held to discuss the confirmatory evidence that included eight in vitro and three in vivo studies not previously submitted to the IND or NDA. Discussions also included new descriptive analyses of the available clinical data including subgroup analyses and long-term data as supporting clinical evidence. The FDA provided guidance on the importance of bridging functional endpoints in an animal model to relevant objective outcomes measured in the pivotal clinical trial.

On December 21, 2023, NDA 214927 was resubmitted as an amendment to the original NDA addressing the deficiencies raised by the FDA in the CRL and the subsequent meetings. The NDA resubmission presents additional evidence and analyses to provide substantial evidence of effectiveness in line with the FDA draft guidance issued in September 2023, *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*. The resubmission included the results from the completed 4-year OLE phase of Study 002, as well as eight in vitro and three in vivo studies not previously submitted to the IND or NDA.

4.2 Clinical Development Program

An overview of the clinical development program for arimoclomol is presented in Table 7. A total of 874 individuals have received ≥ 1 dose of arimoclomol across all clinical programs, including 668 participants in clinical studies and 206 patients in the EAP.

The clinical pharmacology package consists of data from 11 clinical pharmacology trials that evaluated the pharmacokinetics (PK) and/or pharmacodynamics (PD) of arimoclomol. In the single-dose trials, arimoclomol was dosed in the range of 31 mg to 496 mg arimoclomol and in the multiple dose trials, in the range of 62 mg t.i.d. (186 mg/day) to 372 mg t.i.d. (1,116 mg/day).

In NPC, two clinical studies relevant to efficacy were conducted:

- One observational study (with no arimoclomol administered) to characterize the individual patient disease progression profile (Study 001).
- One Phase 2/3 trial to evaluate efficacy and safety of arimoclomol (Study 002). The trial consisted of a placebo-controlled, double-blind treatment phase (12 months) followed by an OLE phase (4 years). In the double-blind phase of Study 002, 34 patients received 372 mg/day (weight-adjusted doses) arimoclomol and 16 patients received placebo.

The NDA submission is supported by safety data from trials with arimoclomol in 3 other distinct indications: Amyotrophic Lateral Sclerosis (ALS), Inclusion Body Myositis (IBM), and Gaucher Disease (GD).

Table 7: Clinical Development Program of Arimoclomol

Study Type Indication Study Identifier:	Study Design; Number of Participants	Status
Clinical Trials in Patients with NPC		
Study 002 (Pivotal Phase 2/3)	Randomized, DB, placebo-controlled for 12 months, followed by OLE up to 4 years, and sub-study (ages < 2 years); N=50	DB: Completed OLE: Completed Sub-study: Ongoing
Study 001 (Observation only / natural history)	Observational, disease progression; N=36	Completed
Clinical Trials in Other Indications		
Amyotrophic lateral sclerosis (ALS)		
AALS-001	Randomized, DB, placebo-controlled (PK and cerebrospinal fluid penetration); N=84	Completed
AALS-001OL	OLE of AALS-001; N=69	Completed
ALS-SOD1	Investigator-initiated, randomized, DB, placebo-controlled; N=38	Completed
ORARIALS-01	Randomized, DB, placebo-controlled; N=245	Completed
ORARIALS-02	OLE of ORARIALS-01; N=120 (terminated early)	Completed
Inclusion body myositis (IBM)		
IBM-10656	Investigator-initiated, randomized, DB, placebo-controlled; N=24	Completed
IBM-4809	Randomized, DB, placebo-controlled; N=152	Completed
IBM-OLE	OLE of IBM4809; N=121	Completed
Gaucher disease (GD)		
ORARIGAU-01	Randomized, DB, placebo-controlled, followed by OLE; N=39	Completed
Clinical Pharmacology		
Single-dose trials		
40338	Single-ascending dose; N=18	Completed
AALS-002	Absorption, metabolism, and excretion; N=6	Completed
AALS-004; AALS-011	Bioavailability and food interaction; N=18 (AALS-004); N=20 (AALS-011)	Completed
OR-ARI-REN-01	Renal impairment; N=30	Completed
OR-ARI-HEP-01	Hepatic impairment; N=24	Completed
Multiple-dose trials		
40343*; AALS-005*	Multiple-ascending dose; N=18 (40343); N=40 (AALS-005)	Completed
AALS-010	Renal safety; N=16	Completed
OR-ARI-MET-01	Multiple-dose PK of arimoclomol and metabolites; N=6	Completed
OR-ARI-TQT-01	QT/QTc interval prolongation; N=34	Completed

* Some multiple dose trials included an initial single dose.
ALS = Amyotrophic Lateral Sclerosis; DB = double-blind; GD = Gaucher disease; IBM = Inclusion Body Myositis; NPC = Niemann-Pick disease, type C; OLE = open-label extension; PK = pharmacokinetic; QTC = corrected QT.

4.3 Nonclinical Development

Arimoclomol has been studied in a comprehensive battery of nonclinical studies including pharmacology, PK, and toxicology. The package also included a core battery of safety pharmacology studies including the assessment of cardiovascular and central nervous system (CNS) effects, as well as respiratory function. Overall, these nonclinical studies are supportive of arimoclomol's MOA, the clinical effects demonstrated in patients with NPC, and the long-term safe use of arimoclomol to treat NPC.

The primary PD studies that have been conducted to investigate the MOA of arimoclomol comprise nine in vitro (Section 7.2.1) and six in vivo (Section 7.2.2) studies. PK parameters of arimoclomol were evaluated, including exposure, absorption, distribution, metabolism, excretion, metabolism, and drug-drug interaction. (Additional details provided in Section 5.1).

5. Clinical Pharmacology

Summary

- Arimoclomol exhibits dose-proportional PKs
  - Peak plasma concentration is reached within 0.25 to 3 hours
  - Steady-state concentrations are usually achieved in 24 hours with 3× daily dosing.
- Arimoclomol is eliminated by both renal clearance and metabolism.
- Arimoclomol is metabolized through the glutathionation, O-glucuronidation, and N-O cleavage pathways.
- The potential for other drugs to significantly affect the systemic exposure to arimoclomol and for arimoclomol to significantly affect the systemic exposure to other drugs is considered low.

5.1 Pharmacokinetics

5.1.1 Absorption

Arimoclomol exhibits dose-proportional PKs. The absolute bioavailability was not investigated, but data from the human absorption, metabolism, and excretion trial indicated high permeability and extensive absorption. The peak plasma concentration was reached within 0.25 to 3 hours. Exposure to arimoclomol increased dose proportionally following single oral administration over the dose range of 31 to 496 mg and multiple 3 times daily doses over the dose range of 62 to 372 mg three times daily (186 to 1,116 mg/day). No relevant effect of food on the PK of arimoclomol was observed.

5.1.2 Distribution

The mean apparent volume of distribution is approximately 230 L, which indicates extravascular distribution. Binding of arimoclomol to plasma proteins is low (approximately 10%), and the binding appears to be independent of the arimoclomol plasma concentration.

5.1.3 Metabolism

Arimoclomol is metabolized through glutathionation, O-glucuronidation, and N-O (oxime) cleavage. The most abundant metabolites circulating in humans at steady state are the cysteine-conjugate of arimoclomol formed following hydrolysis of the glutathione-conjugate, the O-glucuronide, and the cleavage product formed following N-O-cleavage of arimoclomol. None of these 3 most abundant metabolites contribute to the observed pharmacological effects of arimoclomol.

5.1.4 Excretion

Arimoclomol is eliminated by renal clearance and by metabolism. Arimoclomol undergoes active renal secretion via MATE1 and MATE2-K transporters. The mean oral clearance of arimoclomol was approximately 40 L/h, and the apparent elimination half-life was approximately 4 hours.

After a single oral dose of [^{14}C]-arimoclomol, 89.5% of drug-related material was recovered, 77.5% in urine and 12.0% in feces. Approximately 42% of the dose was excreted as parent drug in the urine.

5.1.5 Effects of Sex, Weight, Age and Race

The PK analysis suggested that age did not have a significant effect on the PK of arimoclomol in adults. Sex and body weight were found to be significant covariates affecting the exposure of arimoclomol in adults. However, their effects are likely related to the fixed dosing regimen in adults, with increased clearance with increasing body weight, and with females generally having a lower body weight than males. The observed effects of sex ($AUC_{0–8}$: 23.5% higher in females) and body weight ($AUC_{0–8}$: 15% lower in adults above the median of 78.2 kg) in adults are modest and not considered clinically relevant.

Consequently, no dose adjustment of arimoclomol based on sex or age is necessary. In addition, the same fixed dosing regimen can be administered to all patients weighing > 55 kg.

5.2 Drug-drug Interactions

Because no single biotransformation pathway is responsible for > 25% of arimoclomol's elimination, the potential for other drugs to significantly affect the metabolism arimoclomol is considered low.

Arimoclomol was shown to be a substrate of the MATE1 and MATE2-K transporters in vitro and undergoes active renal secretion. The clinical significance is considered low due to the low likelihood of concomitant use of MATE inhibitors in the NPC population. In addition, arimoclomol is not a drug with a narrow therapeutic index and no signs of renal toxicity have been observed in the completed clinical trials with arimoclomol. Furthermore, inhibition of MATE transporters is not expected to impact tissue distribution or cause clinically relevant changes in drug concentration at the site of action.

Arimoclomol is not an inducer of cytochrome P450 (CYP) enzymes and while it is a weak CYP2D6 inhibitor, its potential of in vivo drug-drug interactions due to inhibition of CYP enzymes is negligible even at the highest recommended dose (372 mg/day).

Based on the results of the in vitro transporter inhibition studies, arimoclomol does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, or OAT3. Weak inhibition by arimoclomol was found at MATE1, MATE2-K, and OCT2, but the potential for in vivo drug-drug interactions was determined to be low at clinical doses.

5.3 Dose Justification and Posology

The dose of arimoclomol in Study 002 was assigned to patients based on their body weight and ranged from 93 to 372 mg/day, as shown in Table 8. The administered dose was scaled to achieve exposure levels in all patients that were approximately equivalent to those achieved in adults at a dose of 372 mg/day (with body weight = 70 kg). Based on the approximately 4-hour half-life of arimoclomol, three-times daily dosing (t.i.d.) was established to maintain a stable plasma concentration throughout the day.

Table 8: Dosing Regimen Used Study 002

Patient Body Weight (kg):	Investigational Dose in Study 002
8 to 15	31 mg t.i.d. (93 mg/day)
>15 to 22	47 mg t.i.d. (140 mg/day)
>22 to 38	62 mg t.i.d. (186 mg/day)
>38 to 55	93 mg t.i.d. (279 mg/day)
>55	124 mg t.i.d. (372 mg/day)

t.i.d. = 3 times a day.

The doses used in Study 002 resulted in a clinically relevant treatment effect, as assessed by the primary 4D-NPCCSS endpoint analysis (Section 6.8.4.1), and the doses were well-tolerated. However, in subsequent communications with the FDA, it was determined that the original dose regimen from Study 002 (Table 8) resulted in sub-optimal arimoclomol exposure in patients with lower body weights.

To optimize exposure in patients with lower body weight, and in consideration of predicted exposure data from an updated population PK study, the lowest dose administered (31 mg t.i.d.) was removed, and the body weight ranges were adjusted to provide similar exposure across all weight groups. Those adjustments constitute the recommended dose (Table 6; Section 3.2), based on the efficacy (Section 6) and safety (Section 7) results of Study 002.

Based on population PK analyses, there are no specific dose-modification recommendations with regards to dosage form (per oral capsule versus dispersed powder in liquid or soft food versus gastrointestinal tube)

6. Clinical Efficacy

Summary

- In Study 002, arimoclomol treatment resulted in clinically meaningful and statistically significant reductions in NPC disease progression in a very heterogeneous patient population.
- In the double-blind phase, the primary efficacy endpoint analysis showed a smaller mean increase in 4D-NPCCSS score (reflecting a significant reduction in disease progression) of 0.62 vs 2.12 for arimoclomol vs placebo.
    - The treatment difference (least-squares mean) was clinically meaningful and statistically significant: -1.51 (95% CI: -2.95, -0.06; p=0.0413).
    - Difference in percent change from baseline 4D-NPCCSS scores also favored arimoclomol with statistical significance: -35.1% (95% CI: -61.3%, -8.8%; p=0.0101).
    - Multiple sensitivity analyses confirmed the robustness of these results, including ANCOVA, MMRM, and Wilcoxon rank sum test.
- The overall results from Study 002 demonstrated significant, clinically meaningful slowing in NPC disease progression and stabilization of NPC symptoms with arimoclomol treatment in a heterogeneous population of patients with NPC.

6.1 Overview of Clinical Studies Relevant to Efficacy

An overview of Studies 001 and 002 is presented in Table 9.

Table 9: Overview of Studies Contributing to the Efficacy Evaluation

Study:	Design	Key Inclusion Criteria	Dose, Regimen, and Number of Patients	Initiation and Completion Dates
Study 001	Observational, non-therapeutic, multisite, multinational, 6- to 14-month observation period 12 sites in 7 countries: 1 in Denmark, 2 in Germany, 4 in Italy, 1 in Poland, 1 in Spain, 1 in Switzerland 2 in the United Kingdom	Confirmed diagnosis of NPC (mutation in *NPC1* or *NPC2* gene) Age 2 to 18 years	NA (observational) 36 patients enrolled (27 of whom continued into Study 002)	October 2015 to May 2017
Study 002	DB, randomized, placebo-controlled, multisite, multinational, 12-month DB treatment, followed by up to 4 years OLE DB: 14 sites in 9 countries: 1 Denmark, 2 France, 2 Germany, 2 Italy, 1 Poland, 1 Spain, 1 Switzerland, 2 United Kingdom, 2 US OLE: 15 sites in 9 countries: 1 Denmark, 1 France, 2 Germany, 2 Italy, 1 Poland, 1 Spain, 1 Switzerland, 4 United Kingdom, 2 US	Participation in Study 001 or confirmed diagnosis of NPC (mutation in *NPC1* or *NPC2* gene) Age 2 to 18 years	93-372 mg/day arimoclomol based on body weight 50 patients enrolled 2:1 in DB phase 41 patients enrolled in OLE phase Capsules for oral administration, t.i.d.	DB: June 2016 to June 2018 OLE: June 2017 to June 2022

DB = double-blind; IMP = investigational medicinal product; NA = not applicable; NPC = Niemann-Pick disease, type C; OLE = open-label extension; t.i.d. = 3 times a day.

6.2 Study 001 (Natural History) Design

Study 001 was a prospective, multi-center, observational, non-therapeutic study in patients with NPC conducted to investigate disease progression in patients with NPC. Patients remained on their routine clinical care therapy, including concomitant medications. Patients were followed for a minimum of 6 months and up to 14 months. All patients completing the study were offered enrollment into the randomized, double-blind, placebo-controlled Study 002.

6.3 Study 002 (Pivotal Phase 2/3) Design

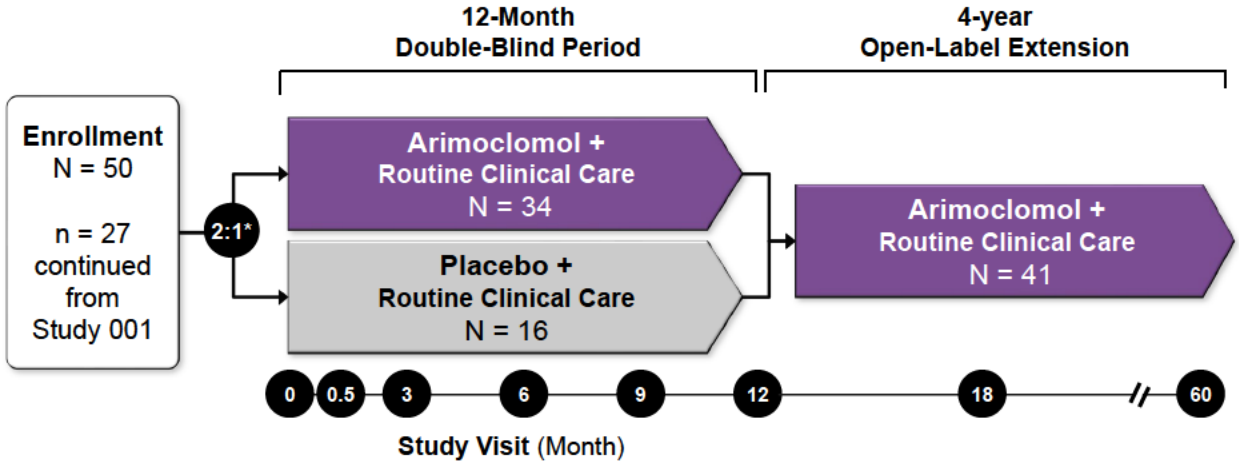
Study 002 was a double-blind, randomized, placebo-controlled, multi-national Phase 2/3 trial conducted to evaluate the efficacy and safety of arimoclomol when administered in addition to current clinical care.

The study included a 12-month double-blind treatment phase in which enrolled patients were randomized 2:1 to receive arimoclomol or placebo. Randomization was stratified by use of miglustat. The double-blind phase was followed by an OLE phase (4 years) where all patients received arimoclomol (Figure 15).

During the 12-month double-blind treatment phase, efficacy assessment of the primary endpoint (4D-NPCCSS) was performed at baseline and after 3, 6, 9, and 12 months of treatment. All other efficacy assessments were performed after 6 and 12 months of treatment. During the OLE phase, efficacy was assessed every 6 months.

The dose of arimoclomol in Study 002 was assigned to patients based on their body weight. The administered dose was scaled to achieve exposure in all patients that is approximately equivalent to the exposure in adults dosed with 372 mg/day (with body weight = 70 kg). Based on the half-life of arimoclomol of approximately 4 hours, t.i.d. dosing was applied to maintain sustained plasma exposure throughout the day.

Figure 15: Study 002 Design



6.4 Enrollment Criteria

Eligibility criteria sought to balance recruitment feasibility of a sufficiently broad and representative patient population in this very rare condition with the need to include a population that was also likely to exhibit some level of progression over 12 months.

Patient enrollment criteria were the same for Studies 001 and 002:

- Aged 2 to 18 years
- Confirmed diagnosis of NPC
- Genetically confirmed (deoxyribonucleic acid [DNA] sequence analysis) by mutations in both alleles of *NPC1* or *NPC2*, or mutation in only one allele of *NPC1* or *NPC2* plus either positive filipin staining or elevated cholestane-triol/oxysterols (> 2 × upper limit of normal [ULN])
- At least one NPC-related neurological symptom at the time of screening
- Ability to walk either independently or with assistance.

Miglustat use was permitted if patients had remained on a stable dose for ≥ 6 months before entering the trial.

Patients were excluded if they exhibited: uncontrolled epilepsy, severe hepatic insufficiency (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] > 3 × ULN for age and sex), renal insufficiency (serum creatinine > 1.5 × ULN), historic or planned liver transplants, or other severe disease manifestations that would inhibit compliance.

Patients who completed Study 001 were eligible for enrollment in Study 002.

6.5 Clinical Endpoints

Endpoints were specified based on FDA guidance and prior to unblinding in Study 002, and included disease-specific (Section 6.5.1) and non-disease-specific (Section 6.5.2) endpoints:

6.5.1 NPC-specific Endpoints

6.5.1.1 NPC Clinical Severity Scale (NPCCSS Endpoint)

The NPCCSS is an NPC disease-specific ClinRO assessment tool developed by the NIH specifically to assess clinical severity and disease progression in NPC patients. The original NPCCSS scale comprises 17 clinical domains relevant to NPC, which are subcategorized into nine major domains and eight minor domains (Yanjanin et al., 2010):

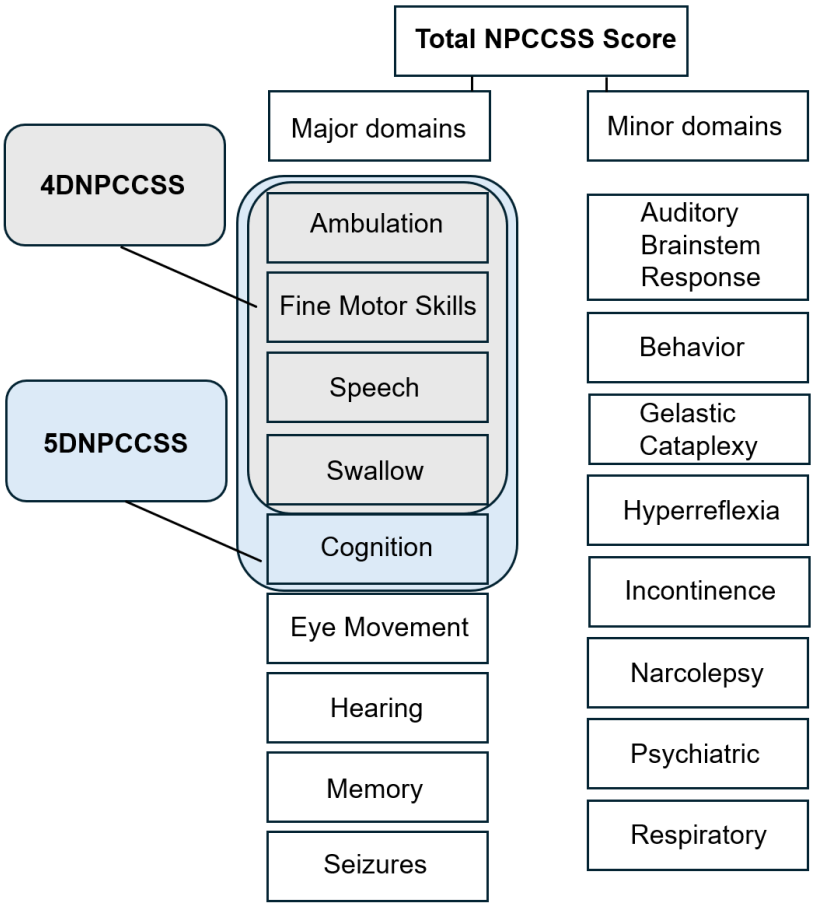
- **Major domains** include eye movements, ambulation, speech, swallow, fine motor skills, cognition, hearing, memory, and seizures
- **Minor domains** include gelastic cataplexy, narcolepsy, behavior, psychiatric, hyperreflexia, incontinence, auditory brainstem response, and respiratory.

In the original NDA submission, and in response to regulatory advice from FDA and European Medicines Agency (EMA), an abbreviated 5-domain NPCCSS was developed to focus on the most important domains and included as the primary endpoint in the protocol and Statistical Analysis Plan (SAP) for Study 002. Domains of the 5D-NPCCSS from the original submission included ambulation, fine motor skills, speech, swallow, and cognition.

Following the CRL, and in response to further regulatory advice from FDA, the cognition domain was removed from the 5D-NPCCSS. In addition, the scoring methodology for the swallow domain was revised without altering the scoring categories reported during the trial. Following these changes, the resulting 4D-NPCCSS was used as primary endpoint for analysis in Study 002. The 4D-NPCCSS comprises the four domains of ambulation, fine motor skills, speech, and swallow.

Figure 16 provides an overview of the clinical domains from the 17-domain, 5-domain, and 4-domain NPCCSS. Table 10 shows the scoring criteria for the 4D-NPCCSS, which was used as the primary endpoint to assess efficacy of arimoclomol in the present NDA resubmission, in alignment with FDA's recommendation.

Figure 16: NPC Clinical Severity Scale (NPCCSS)



4DNPCCSS = 4-domain NPCCSS; 5DNPCCSS = 5-domain NPCCSS.

Table 10: Scoring of Key NPCCSS Domains (4D-NPCCSS)

Domain:	Scoring Criteria	Score Range[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
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
Swallow	**Swallow Response Category** / **Updated** / **Original** 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	0–5
Total Score	Sum of all scores of the following domains with the systematic review scoring methodology for the swallow domain: ambulation, fine motor skills, swallow, speech	0–20

a. Higher score = more severe clinical impairment.
Note: the scoring categories of the swallow domain that were assigned a revised score value following FDA's recommendation are shaded in light gray.

6.5.1.1.1 4D-NPCCSS Validation

The 4D-NPCCSS consists of the following four domains: ambulation, fine motor skills, speech, and updated swallow. Most of the validation work was performed with the five domains of the 5D-NPCCSS before systematic review of the scoring methodology for the swallow domain and removal of the cognition domain. The updated swallow domain does not invalidate the instrument because descriptors of the scoring categories remain consistent and unaltered, which maintains integrity of rater assessments. Thus, only the severity score within each category was

adjusted to better match the swallow impairment progression of patients with NPC. (See Table 10 in Section 6.5.1.1 for additional scoring details.)

The original scoring methodology for the swallow domain created equivalencies among unequal states of disease progression and severity. For example, under the original scoring methodology, a patient who did not require a feeding tube but experienced dysphagia with liquids and solids would be given the same maximum score as a patient who required a feeding tube for all nutrition. Based on input from the FDA, a Qualitative Study with NPC and swallow clinical experts was conducted to gather additional data to support the overall validity and reliability of the NPCCSS instrument. The study also informed the updating of the swallow domain to improve its score linearity and alignment of the response categories with disease severity levels and thus, the overall validity and reliability of the instrument. The information obtained in the study confirmed that the response categories captured relevant clinical features in proper order of severity in the swallow domain to track changes over time across ages and thus, allowed for consistent patient assessments in Study 002.

The updated swallow domain scoring methodology simplifies the scoring to reflect linearity in disease progression based on a patient's level of dysfunction. Each stepwise increase in swallow dysfunction matches with numeric increases in score.

The full 4D-NPCCSS along with the descriptions that define each level of increasing severity is shown in Table 11. Note that ambulation, fine motor skills, and speech scales do not take on values for all possible scores between 0 and 5.

Table 11: Definitions and Scoring for Each 4D-NPCCSS Domain

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

To ensure proper standardization and allow for reliable and reproducible scoring of the four pivotal NPCCSS domains, score distributions were compared, and correlation analyses performed with various relevant performance tests as part of the validation work. Although scores cannot be perfectly mapped between performance tests and related NPCCSS domains due to differences in individual score ranges and category descriptors (the scales are intended to

measure different aspects of the disease), moderate to strong correlations (polychoric and Spearman correlations) have been found between the individual four domains of the 4D-NPCCSS and corresponding items on the following performance-based tests:

- Scale for Assessment and Rating of Ataxia (SARA) vs NPCCSS ambulation, speech, and fine motor skills
- Nine-Hole Peg Test (9-HPT) vs NPCCSS fine motor skills
- Interpretative rating scales of the functional swallow test video fluoroscopic swallowing study (VFSS):
    - American Speech-Language-Hearing Association National Outcomes Measurement System (ASHA-NOMS) vs NPCCSS swallow
    - Penetration-Aspiration Scale (PAS) vs NPCCSS swallow.

This work supported that the 4D-NPCCSS domains were appropriately standardized across patients and clinical sites and confirm the validity of the 4D-NPCCSS.

In summary, the qualitative and quantitative data support the content validity, construct validity, and reliability of the 4D-NPCCSS endpoint as a clinical outcome assessment measure in NPC clinical research.

Strong correlations between each of the four domains of the 4D-NPCCSS and relevant performance-based tests support that the 4D-NPCCSS is well-defined and appropriately standardized for use in clinical trials in NPC and provide additional support for the validity of all four domains. The Qualitative Study with NPC and swallow experts supports that the NPCCSS swallow domain could appropriately assess severity progression of swallow dysfunction in Study 002.

6.5.1.1.2 Minimum Clinically Important Difference in NPCCSS

Because the NPCCSS did not have a pre-determined minimal clinically important difference (MCID) meaningful change in 4D-NPCCSS was discussed in interviews with caregivers/patients and clinicians. In the interviews with patients and caregivers, more than 70% of respondents stated that a 1-point change is meaningful in any of the 4D-NPCCSS domains. An even larger proportion of participants (77.8%) indicated that any slowing of disease progression would be meaningful. Therefore, a 1-point change in the 4D-NPCCSS was established as a clinically meaningful threshold.

6.5.1.2 NPC Clinical Database (NPC-cdb)

The NPC Clinical Database (NPC-cdb) score (Stampfer et al., 2013) consists of 10 subject areas: visceral signs, development, motor function, ocular-motor abnormalities, seizures/cataplexy/narcolepsy, cognitive abilities and memory, behavioral and psychiatric abnormalities, speech, hearing, and abilities in daily life. The NPC-cdb score represents both historical symptoms and a current status (Stampfer et al., 2013). The current status questionnaire was simplified for the trial to collect data for a current visit score sum. The score is a severity-weighted sum of 72 symptoms considered as disease-relevant at the time of assessment. Each symptom contributes a score ranging from 1 to 5 with a maximum score of 125 for the total scale. Increases in the NPC-cdb score reflect reductions in the patient's abilities.

6.5.2 Additional Endpoints Not Specific to NPC

Because of the extreme rarity of NPC and the wide heterogeneity of disease symptoms, several non-NPC-specific endpoints were included in the study to provide additional insights into the impacts of NPC disease and potential treatment effects on broad measures of symptoms and quality of life. However, it should be acknowledged that some of these endpoints were not suitable for the entire study population, since some patients could not complete certain assessments due to age appropriateness or advanced disease severity. Additionally, the study did not implement type-I error control for these endpoints due to their exploratory nature. Relevant data from these endpoints (e.g., SARA, 9-HPT) were used to investigate the validity of NPC-specific measures. However, the clinical and statistical limitations preclude drawing meaningful conclusions about treatment effects from these endpoints.

6.6 Statistical Methods

6.6.1 Sample Size

Given the ultra-rare condition and lack of proper reference data, the sample size determination of Study 002 was primarily based on feasibility and not on a formal sample size calculation.

6.6.2 Analysis Sets

No analysis set was defined for the observational Study 001. The dataset included all enrolled patients.

In Study 002, the Full Analysis Set (FAS) was defined as all patients who were randomized and received at least one dose of treatment medication during the double-blind phase. The FAS was used for all efficacy analyses. In the primary analysis used to establish efficacy of arimoclomol based on the while-on-treatment estimand, data from all patients with at least one post-baseline visit were included.

For the OLE phase of Study 002 the Extension Set was defined as all patients who received at least one dose of arimoclomol in the extension phase. The Extension Set was used for all efficacy analyses of patient data from the OLE phase.

6.6.3 Endpoint Analyses

The main analysis set for the efficacy analyses was the FAS.

6.6.3.1 Analyses of the Primary Efficacy Endpoint

The primary disease-specific endpoint of Study 002 was defined as: Change in NPC disease severity based on the 4D-NPCCSS (ambulation, speech, fine motor skills, and updated swallow domains) from baseline to last visit while on treatment.

The primary endpoint was revised from the 5D-NPCCSS to the 4D-NPCCSS endpoint (without the cognition domain and with the updated swallow domain; see Section 6.5.1), and the treatment effect was reassessed using the FDA-preferred while-on-treatment estimand instead of the prespecified hypothetical estimand. See Section 6.6.4 for additional details.

Missing data for the primary endpoint were not imputed. If a baseline value was missing, no change from baseline was calculated.

6.6.4 Estimands

The protocol for Study 002 was initiated and the SAP was finalized (August 2018) prior to adoption of the ICH E9 (R1) addendum on estimands in November 2019 (ICH, 2019). For these reasons, estimands were not included in the SAP. However, the de facto estimand that was prespecified in the SAP and included in the original NDA was a hypothetical estimand. The prespecified primary efficacy endpoint analysis was based on an MMRM model using all observed data obtained prior to onset of escape medication. The reasons for censoring patient data after onset of escape medication were to safeguard against potential bias associated with unblinded assessment of the NPCCSS and to evaluate the treatment difference at 12 months under the assumption that the patients adhered to treatment. The design of Study 002 and the agreed upon primary MMRM analysis based on the hypothetical estimand were originally developed with these objectives. Due to concerns regarding the handling of missing data and clinical plausibility of the assumptions underlying the hypothetical estimand, the FDA requested that the primary efficacy endpoint be reanalyzed using a while-on-treatment estimand in the resubmission.

The while-on-treatment estimand evaluated change in 4D-NPCCSS scores from baseline at the last available visit through 12 months, regardless of blinding. The last visit for patients completing the study was Visit 6 at the end of the double-blind phase. The last value was collected at the respective end-of-study evaluation on the day of withdrawal for patients that discontinued prior to the end of the double-blind phase. For patients who met the early escape criteria, the last-value-while-on treatment was used regardless of blinding (i.e., the last value was collected during open-label treatment).

Early escape for a patient was defined as meeting any one of the following three criteria, as assessed by the investigator with respect to the NPCCSS domains of ambulation, swallowing, and fine motor skills:

1. An increase of at least 2 points simultaneously in two out of the three relevant domains of the NPCCSS (for at least 4 points in total) within a period of 3 months
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
3. An increase of at least 2 points simultaneously in all of the three relevant domains of the NPCCSS (for at least 6 points in total) within a period of 6 months.

6.6.5 Sensitivity Analyses

Several sensitivity analyses were performed to evaluate change from baseline in the 4D-NPCCSS endpoint. In one sensitivity analysis, the primary analysis was repeated with a slightly more restrictive but potentially less biased while-on-blinded treatment estimand. The 4D-NPCCSS endpoint was also evaluated using the pre-specified analysis using the MMRM model previously described. In addition, a non-parametric Wilcoxon rank sum test was conducted to reduce the impact of potential influential/outlying values.

6.7 Study 001 (Natural History) Results

6.7.1 Study 001 Patient Disposition

A total of 36 patients with NPC were enrolled in the study, of whom 31 completed and five withdrew (Table 12). Twenty-seven patients entered Study 002 after completing Study 001.

Table 12: Study 001: Patient Disposition (All Enrolled Patients)

Disposition, n (%):	Total (N=36)
Completed	31 (86.1)
Early withdrawal	5 (13.9)
Reason for early withdrawal	
Protocol violation	1 (2.8)
Lost to follow up	1 (2.8)
Other[a]	3 (8.3)
Entered Study 002 after completing Study 001	27 (75.0)

a. One patient moved to the United States; one discontinued due to progression, and one withdrew early for an unknown reason.

6.7.2 Study 001 Demographics and Baseline Characteristics

Baseline demographics (Table 13) and medical characteristics (Table 14) were reflective of the patient population with NPC. The mean age at baseline was 9.9 years, and there was an even distribution of female and male participants. All 36 enrolled patients had an NPC diagnosis with mutations in *NPC1*, and all patients had a history of neurological symptoms.

Table 13: Study 001: Demographics (All Enrolled Patients)

Demographic, n (%):	Total (N=36)
Age, years (SD)	9.9 (4.6)
Age groups	
< 4 years	5 (13.9)
4 to < 8 years	6 (16.7)
8 to < 12 years	13 (36.1)
≥ 12 years	12 (33.3)
Gender	
Male	15 (41.7)
Female	21 (58.3)
Race	
White	33 (91.7)
Other	3 (8.3)

SD = standard deviation

Table 14: Study 001: Baseline Medical Characteristics

Baseline Characteristic:	Total (N=36)
NPC1 diagnosis, n (%)	36 (100)
Time since first NPC symptom (years), mean (SD)	6.7 (3.70)
Currently treated with miglustat, n (%)	
Yes	30 (83.3)
No	6 (16.7)
NPCCSS	
4D-NPCCSS score, mean (SD)	6.8 (5.0)
Individual NPCCSS domains scores, mean (SD)	
Ambulation	2.0 (1.5)
Speech	1.6 (1.2)
Swallow	1.1 (1.6)
Fine motor skills	2.0 (1.6)
Body-mass index, mean (SD)	18.1 (2.6)

ABR = auditory brainstem response; NPCCSS = Niemann-Pick Disease, type C Clinical Severity Scale; 4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale with updated swallow domain; SD = standard deviation.

6.7.3 Study 001 Findings

Over the 6–14 months observation period, the mean (SD) score for the 4D-NPCCSS increased by 1.4 (2.4) points from 6.8 (5.0) points at Baseline to 8.0 (5.6) points at Visit 2. The individual domain scores increased, except for the mean cognition score that did not change in 12 months. Overall, these observations show the natural progression of NPC, and support an MCID of $\geq$ 1 point change on the NPCCSS endpoint.

Table 15: Study 001: Change from Baseline in Clinical Status Assessments (All Enrolled Patients)

Instrument Score, mean (SD):	Baseline (N=36)	Visit 2 (N=32)*	Change from Baseline (N=32)*
4D-NPCCSS score	6.8 (5.0)	8.0 (5.6)	1.4 (2.4)
Individual domains scores			
Ambulation	2.0 (1.5)	2.2 (1.7)	0.3 (0.7)
Speech	1.6 (1.2)	2.0 (1.4)	0.3 (0.9)
Swallow	1.1 (1.6)	1.3 (1.7)	0.3 (0.7)
Fine motor skills	2.0 (1.6)	2.5 (1.8)	0.4 (1.1)

* The number of patients contributing with Visit 2 data (N=32) differs from the number of completers (N=31; Table 12) because 1 of the withdrawn patients had End of Trial/Visit 2 assessments on the day of withdrawal.
NPCCSS = NPC Clinical Severity Scale; SD = standard deviation.

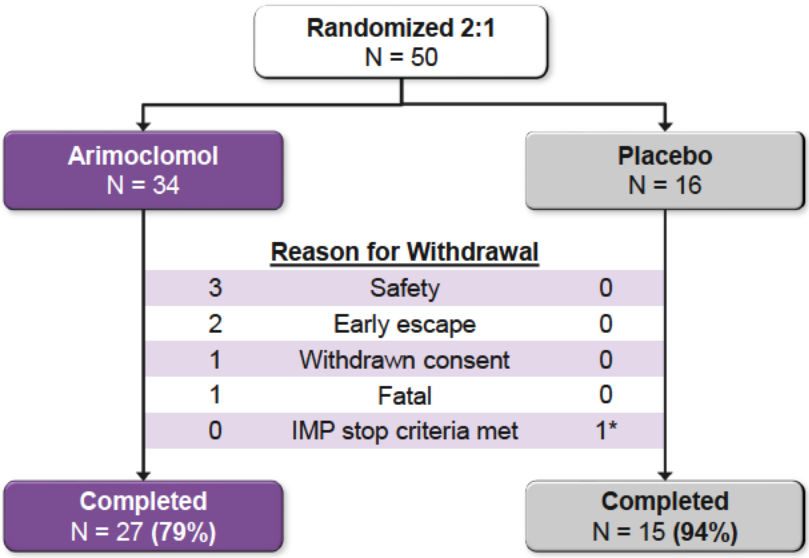
6.8 Study 002 (Pivotal Phase 2/3) Results

6.8.1 Study 002 Patient Disposition

A total of 50 patients, including 27 patients from Study 001, were randomized and dosed in Study 002: 34 patients to the arimoclomol group and 16 patients to the placebo group (Figure 17). Forty-two (42) patients completed the blinded phase of the trial (27 arimoclomol; 15 placebo). Seven patients in the arimoclomol group and one in the placebo group withdrew

from the blinded phase. In the arimoclomol group, two patients were assigned to early escape during the trial.

Figure 17: Study 002: Patient Disposition



*Worsening of epilepsy after initial placebo dose.
IMP = investigational medicinal product.

6.8.2 Study 002 Demographics

Overall, demographic baseline characteristics in Study 002 including age, sex, race, and body mass index were representative of children and adolescents with NPC (Table 16). Approximately half of patients were female, and most patients were white.

Table 16: Study 002: Demographics – Double-blind Phase (FAS)

Demographic, n (%):	Arimoclomol (N=34)	Placebo (N=16)
Age, mean (SD)	11.5 (5.4)	10.2 (4.1)
Age group, n (%)		
< 4 years	4 (11.8)	2 (12.5)
4 to < 8 years	6 (17.6)	1 (6.3)
8 to < 12 years	6 (17.6)	8 (50.0)
≥ 12 years	18 (52.9)	5 (31.3)
Gender, n (%)		
Male	17 (50.0)	7 (43.8)
Female	17 (50.0)	9 (56.3)
Race, n (%)		
White	32 (94.1)	13 (81.3)
Other	2 (5.9)	3 (18.8)
BMI, mean (SD)	18.7 (4.2)	19.5 (3.3)

BMI = body mass index; FAS = full analysis set; SD = standard deviation.

6.8.3 Study 002 Baseline Disease Characteristics

For the baseline disease characteristics, the mean NPCCSS scores were higher in the patients randomized to arimoclomol than in the placebo group (Table 17). All 3 patients with double functional null mutations, predictive of a severe and rapidly progressive disease course, were randomized to the arimoclomol group. These 3 patients were all younger than 4 years of age, and none were receiving miglustat treatment.

The proportion of patients concomitantly receiving miglustat was similar across treatment groups and consistent with the overall NPC population (Geberhiwot et al., 2018; Patterson et al., 2020).

Table 17: Study 002: Baseline Disease Characteristics – Double-blind Phase (FAS)

Baseline Characteristic, measure:	Arimoclomol (N=34)	Placebo (N=16)
NPC1 diagnosis, n (%)	34 (100)	16 (100)
Time since first NPC symptom, mean years (SD)	7.6 (4.5)	8.1 (3.8)
Age at onset of first neurological symptom, mean years (SD)	5.1 (3.4)	5.2 (3.9)
Age at first neurological signs, mean years (SD)		
Pre/peri-natal (< 3 months)	1 (2.9)	0
Early infantile (3 months to < 2 years)	5 (14.7)	3 (18.8)
Late infantile (2 to < 6 years)	17 (50.0)	7 (43.8)
Juvenile (6 to 15 years)	11 (32.4)	6 (37.5)
Currently treated with miglustat, n (%)		
Yes	26 (76.5)	13 (81.3)
No	8 (23.5)	3 (18.8)
4D-NPCCSS score, mean (SD)	9.2 (5.8)	6.7 (5.2)
Individual domains scores, mean (SD)		
Ambulation	2.5 (1.6)	2.2 (1.6)
Fine motor skills	2.8 (1.8)	1.9 (1.8)
Speech	2.2 (1.6)	1.6 (1.2)
Swallow	1.8 (1.6)	1.1 (1.4)
Patient genotype, n (%)		
Double functional null	3 (8.8)	0 (0)
Double missense	16 (47.1)	11 (68.8)
Missense / functional null	15 (44.2)	5 (31.3)

FAS = full analysis set; N = number of patients in population; 4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale with the updated swallow domain; SD = standard deviation.

6.8.4 Study 002 Efficacy Results

6.8.4.1 Primary Endpoint: 4D-NPCCSS Change from Baseline

The primary efficacy endpoint analysis showed a mean (SE) change in 4D-NPCCSS score (disease progression) of 0.62 (0.39) in the arimoclomol group vs 2.12 (0.59) for placebo, representing a clinically meaningful and statistically significant treatment effect in favor of arimoclomol over placebo of -1.51 points (95% CI: -2.95, -0.06; p=0.0413) (Table 18). Plots of the mean changes in 4D-NPCCSS score from baseline over time are shown in Figure 2.

Table 18: Study 002: Primary Endpoint Analysis of Change in 4D-NPCCSS from Baseline to Last Visit while on Treatment Using an ANCOVA Model (FAS)

	Change from Baseline at Month 12			
Primary Endpoint:	**Arimoclomol (N=34)**	**Placebo[a] (N=15)**	**LSM Difference (95% CI)**	**p-value**
4D-NPCCSS, points (SE)	0.62 (0.39)	2.12 (0.59)	-1.51 (-2.95, -0.06)	0.0413

a. One placebo patient with no post-baseline data is excluded from the analysis.
ANCOVA model included treatment and miglustat as fixed effects, and baseline 4D-NPCCSS score as covariate.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; LSM = least squares mean; SE = standard error.

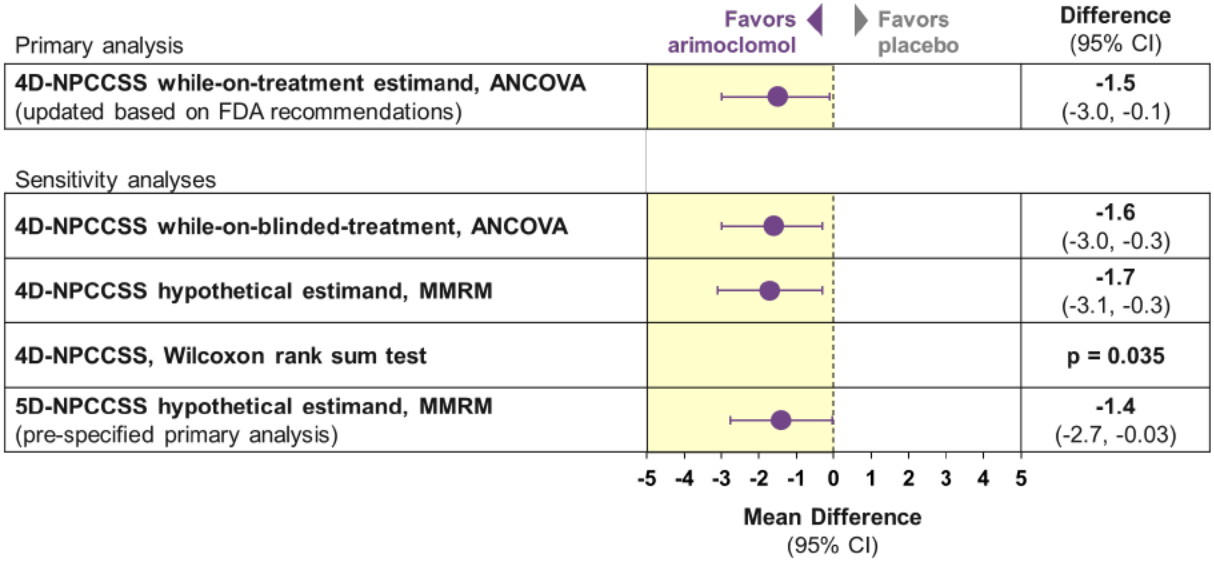
Importantly, the arimoclomol group included more patients with severe disease at baseline and all three patients with rapidly progressing double null *NPC1* mutation vs no patients in the placebo group. (See Section 6.8.3 for additional details.)

The primary analysis was repeated with percent change in raw 4D-NPCCSS score from baseline at the last visit using the same while-on-treatment principle. The estimated increase in 4D-NPCCSS score from baseline was 14.9% and 50.0% for arimoclomol and placebo, respectively, with a corresponding statistically significant treatment difference of -35.1% (95% CI: -61.3%, -8.8%; p=0.0101).

6.8.4.2 Sensitivity Analyses

Sensitivity analyses were performed with the endpoint change from baseline in 4D-NPCCSS score. The analyses supported findings of the primary efficacy endpoint analysis (Figure 18).

Figure 18: Study 002: Sensitivity Analyses of Primary Endpoint – Double-blind Phase (FAS)

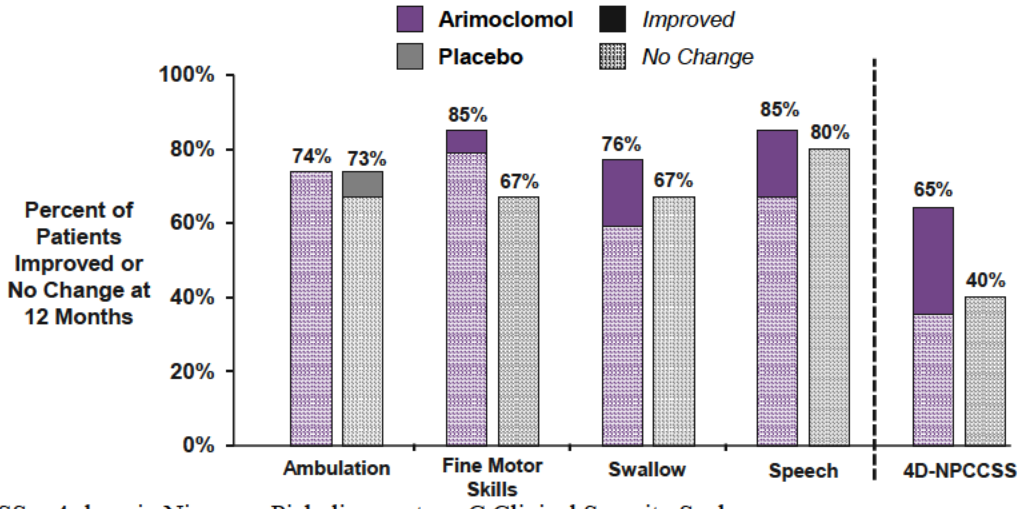


4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; 5D-NPCCSS = 5-domain Niemann-Pick disease, type C Clinical Severity Scale; ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; MMRM = mixed effects model for repeated measurements.

6.8.4.3 Responder Analyses

Figure 19 presents the proportion of patients with improved or no change from baseline to 12 Months in individual 4D-NPCCSS domains. The responder rate with arimoclomol treatment was numerically higher for all four domains; differences were greatest in the fine motor skills and updated swallow domains.

Figure 19: Study 002: Responder Analysis by Domain (Double-blind Phase)



4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale.

6.8.4.4 NPC Clinical Database (NPC-cdb)

The mean (SD) Baseline score was higher in the arimoclomol group (N=32) vs placebo (N=16): 46.5 (24.0) points vs 39.2 (28.6), respectively.

The mean difference in change from Baseline in NPC-cdb points (95% CI) numerically favored arimoclomol at 6 and 12 months but did not achieve statistical significance: -5.09 (-10.26, 0.08; p=0.0536) at 6 months and -3.03 (-9.90, 3.85; p=0.3785) at 12 months for arimoclomol vs placebo.

6.9 Clinical Efficacy Conclusions

Consistent with the results from the in vitro and in vivo studies, Study 002 demonstrated a clear clinically meaningful and statistically significant treatment difference in change from 4D-NPCCSS baseline score between arimoclomol and placebo in the primary endpoint analysis based on the while-on-treatment estimand as recommended by the FDA. Patients randomized into the arimoclomol group experienced a slower rate of disease progression with stabilization of NPC symptoms during the double-blind phase compared to placebo patients. Slowing disease progression is a clinically relevant outcome for patients and families affected by this fatal and progressive neurodegenerative disease.

Additionally, patients who were switched to arimoclomol treatment in the OLE phase of Study 002 following 1 year of placebo treatment in the double-blind phase, reported a meaningful improvement in NPC progression rate. Importantly, the improved progression rate in these patients remained stable for up to 4 years of open-label treatment. Patients randomized to arimoclomol in the double-blind phase maintained approximately the same progression rate through both study phases for up to 5 years of arimoclomol treatment. A more detailed discussion on this piece of confirmatory clinical evidence is provided in Section 7.1.3.1.

A complementary beneficial effect was observed when miglustat was dosed together with arimoclomol in Study 002. This finding is consistent with the results of the in vitro and animal studies and supports that the in vitro studies identified the mechanistic pathways of arimoclomol, and that the treatment benefits found in the animal studies are directly related to the clinical benefits reported in NPC patients.

7. Confirmatory Evidence of Efficacy

Summary

- Clinical evidence of efficacy from the Open-label Extension Phase of Study 002 confirmed and supported positive findings from the Double-blind Phase
  - Patients who switched from placebo in the double-blind phase to arimoclomol in the OLE had mean 4D-NPCCSS score decrease from 1.9 to 0.3 points/year
  - In the OLE phase, patients continuing arimoclomol treatment maintained a clinically meaningful difference on the 4D-NPCCSS compared with the estimated natural disease progression
- Intrapatient comparison of two independent cohorts changing from 1-year placebo or no treatment to 1-year arimoclomol treatment showed slowed disease progression when receiving arimoclomol
  - Patients who were randomized to arimoclomol in the double-blind phase of Study 002 after participating in Study 001 (routine treatment/no arimoclomol) had mean 4D-NPCCSS score decrease from 1.6 to 0.8 points/year
  - Patients who switched to arimoclomol in the OLE phase of Study 002 after completing the double-blind phase on placebo reported a mean 4D-NPCCSS score decrease from 1.9 to 0.2 points/year
- The in vitro data provide substantial mechanistic evidence of how arimoclomol upregulates expression of CLEAR genes including *NPC1* resulting in higher levels of mature NCP1 protein in the cell.
- The PD studies in 2 different NPC mouse models (*Npc1*$^{-/-}$ and *Npc1*^{nmf164}) show a clear and consistent beneficial effect of arimoclomol on survival and rearing function.
- Arimoclomol promotes lysosomal function, autophagy flux, and clearance of unesterified cholesterol from the lysosomal compartment.
- Consistent with the mechanistic findings of the in vitro studies, the totality of evidence from the in vivo studies shows that arimoclomol produces treatment benefits in animals that are predictive of therapeutic effects in NPC patients.

7.1 Clinical Confirmatory Evidence: Open-label Extension of Study 002

In the open-label extension period of Study 002, all patients who completed the double-blind, placebo-controlled primary efficacy phase were eligible to continue and receive the same weight-based dosing of arimoclomol for up to 4 more years. Clinicians and patients remained blinded to initial randomization assignments from the double-blind phase for at least 2 years so that patients who crossed from placebo to arimoclomol could serve as their own individual controls.

7.1.1 Open-label Patient Disposition

In the following, results are described relative to:

- **Baseline 1**: defined by patient and by variable as the last non-missing value before randomization (blinded phase).
- **Baseline 2**: defined as the last non-missing value before first use of arimoclomol in the extension phase.

Efficacy analyses are presented according to two treatments groups:

- **Arimoclomol-arimoclomol Group**: patients who received arimoclomol during both the double-blind and the OLE phase.
- **Placebo-arimoclomol Group**: patients who received placebo in the double-blind phase and were switched to arimoclomol in the OLE phase.

The OLE phase was conducted at 15 sites in nine European countries and in the US (two of the sites). The patient disposition of the OLE phase including the reason for early withdrawal and 4D-NPCCSS scores is provided in Table 19.

A total of 41 patients continued in the OLE phase (including 23 patients who had previously enrolled in Study 001). A total of 29 patients completed the OLE, and 12 patients withdrew early, including two patients who died during the OLE. Neither death was considered as related to study drug (additional details provided in Section 8.3.4 and narratives in Section 11.1.2). There was no general pattern in 4D-NPCCSS scores that correlated with withdrawal events.

Table 19: Patient Disposition – Open-label Extension Phase of Study 002 (Extension Set)

Open-label Disposition, n (%):	Arimoclomol (N=26)	Placebo (N=15)
Early withdrawal from extension phase	8 (30.8)	4 (26.7)
Reason for early withdrawal from extension phase		
Withdrawal by parent/guardian	4 (15.4)	2 (13.3)
Safety issue	1 (3.8)	1 (6.7)
Physician decision	1 (3.8)	1 (6.7)
Death	2 (7.7)	0

4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale with updated swallow domain.

7.1.2 Open-label Demographics and Baseline Characteristics

Demographics (Table 20) and medical characteristics (Table 21) at Baseline 2 (start of OLE phase) were balanced overall and representative of the patient population.

Table 20: Demographics – Open-label Extension Phase of Study 002 (Extension Set)

Characteristic at Baseline 2, n (%):	Arimoclomol-Arimoclomol (N=26)	Placebo-Arimoclomol (N=15)
Age (years), mean (SD)	12.6 (5.1)	11.5 (4.3)
Age group		
< 4 years	2 (7.7)	0 (0.0)
4 to < 8 years	3 (11.5)	2 (13.3)
8 to < 12 years	6 (23.1)	6 (40.0)
≥ 12 years	14 (53.8)	7 (46.7)
Sex		
Male	13 (50.0)	7 (46.7)
Female	13 (50.0)	8 (53.3)

Characteristic at Baseline 2, n (%):	Arimoclomol-Arimoclomol (N=26)	Placebo-Arimoclomol (N=15)
Race		
White	24 (92.3)	12 (80.0)
Asian	1 (3.8)	1 (6.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (6.7)
Other	1 (3.8)	1 (6.7)

Baseline 2 = last visit of the DB phase of Study 002 (Visit 6).
SD = standard deviation.

However, ages at both the first NPC symptom and first neurological symptom were approximately 1 year younger in the arimoclomol-arimoclomol group, corresponding with a longer time since NPC diagnosis than placebo-arimoclomol patients.

Table 21: Baseline 2 Medical Characteristics – Open-label Extension Phase of Study 002 (Extension Set)

Characteristic at OLE Baseline:	Arimoclomol-Arimoclomol (N=26)	Placebo-Arimoclomol (N=15)
Time since first NPC symptom (years), mean (SD)	7.97 (4.42)	8.48 (3.69)
Time since NPC diagnosis (years), mean (SD)[a]	6.35 (4.45)	5.33 (4.24)
Age at onset of first neurological symptom (years), mean (SD)	4.73 (3.32)	5.37 (3.95)
4D-NPCCSS score, mean (SD)	9.5 (6.7)	8.7 (6.5)
4D-NPCCSS individual domains scores, mean (SD)		
Ambulation	2.8 (1.7)	2.5 (1.8)
Speech score	2.0 (1.6)	1.9 (1.5)
Swallow	1.9 (2.0)	1.8 (1.9)
Fine motor skills	2.8 (1.9)	2.5 (1.7)
Weight (kg), mean (SD)	39.7 (14.5)	41.0 (17.6)

a. N=24 and 14 for arimoclomol and placebo, respectively.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale with updated swallow domain; SD = standard deviation.

7.1.3 Open-Label Efficacy Results

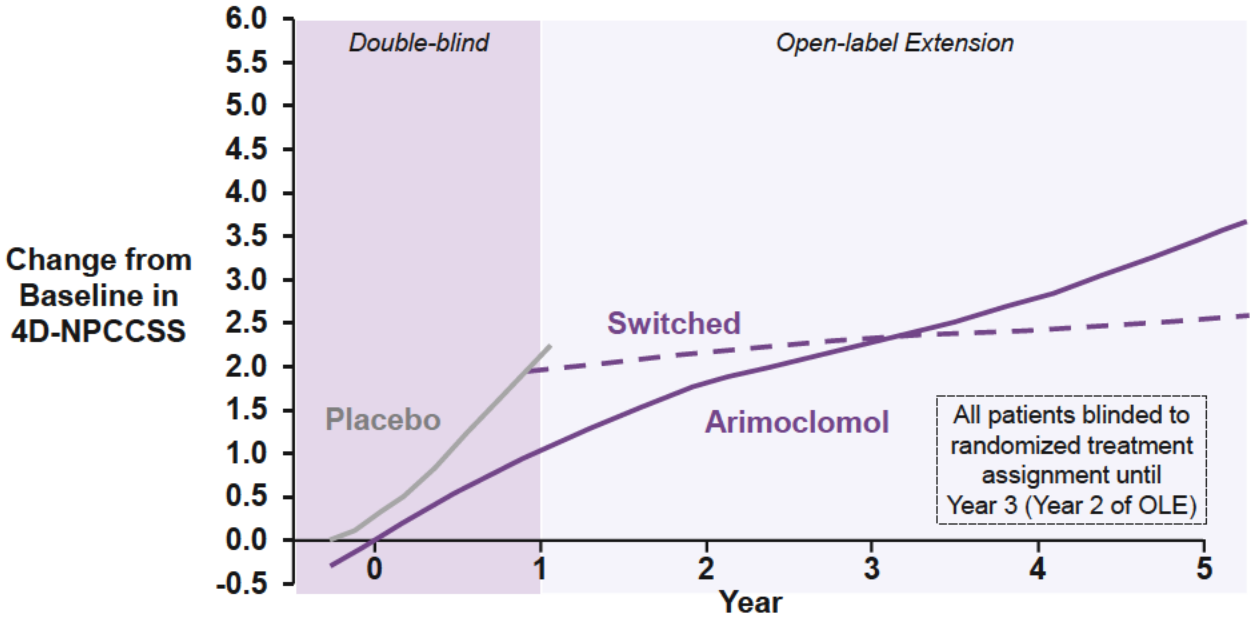
7.1.3.1 4D-NPCCSS and Intra-patient Effect after Switching to Arimoclomol

NPC disease progression as measured by 4D-NPCCSS was compared by treatment group between the double-blind phase and the OLE phase of Study 002. After the double-blind phase during which patients treated with arimoclomol showed disease stabilization compared to placebo patients, patients who switched from placebo to open-label arimoclomol also started to show slowing of disease progression. The annual 4D-NPCCSS score change in placebo-arimoclomol patients decreased from 1.9 points/year during the double-blind phase to 0.3 points/year (1.1 total/4 years) during the OLE phase. The annual change in 4D-NPCCSS from Baseline 2 (OLE Baseline) in arimoclomol-arimoclomol patients that completed the OLE phase was approximately 0.93 points/year (3.7 total/4 years).

NPC progression is visualized with locally estimated scatterplot smoothing (LOESS) plots of the 4D-NPCCSS score changes from Baseline 1 (double-blind Baseline; Figure 20). The data for arimoclomol-arimoclomol patients are shown continuously from Baseline 1 through the end of

the OLE phase. Data for placebo-arimoclomol patients were fit separately for the double-blind phase where patients received placebo and the OLE phase where the same patients were treated with arimoclomol for the remainder of the study.

Figure 20: LOESS Plots of 4D-NPCCSS Score Changes from Baseline 1 – Double-blind and OLE Phase of Study 002 (FAS plus Extension Set)



Arimoclomol	34	27	22	21	20	16
Placebo/Arimoclomol	15	15	12	12	11	9

Arimoclomol = continuous data of arimoclomol patients during DB and OLE phase; Placebo = data of placebo patients collected during DB phase; Switched = patients randomized into the placebo group during the DB phase and switched to arimoclomol at the beginning of the OLE phase.
Data for placebo/switched patients are modeled separately for the DB and the OLE phase. Near the end of the DB phase, some patients were still on placebo while others were already switched to arimoclomol resulting in a small overlap between the two curves.
The sample sizes (N) shown for each study year indicate the number of patients remaining after the respective time point. Since LOESS curves are based on local regression analysis, the N values do not represent the actual number of patients included at each time point.
FAS = Full Analysis Set; LOESS = locally estimated scatterplot smoothing; OLE = open-label extension; 4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale with the updated swallow domain.

The progression rate of placebo patients that switched to arimoclomol after the end of the double-blind phase decreased markedly during the OLE phase. No meaningful change in progression rate was found in the arimoclomol-arimoclomol group after entering the OLE phase indicating that the treatment effect observed in the patients that switched from placebo to arimoclomol was not simply caused by the knowledge of receiving active study drug. Moreover, study participants remained blinded to their randomized treatment (in the double-blind phase) until at least 2 years into the OLE phase.

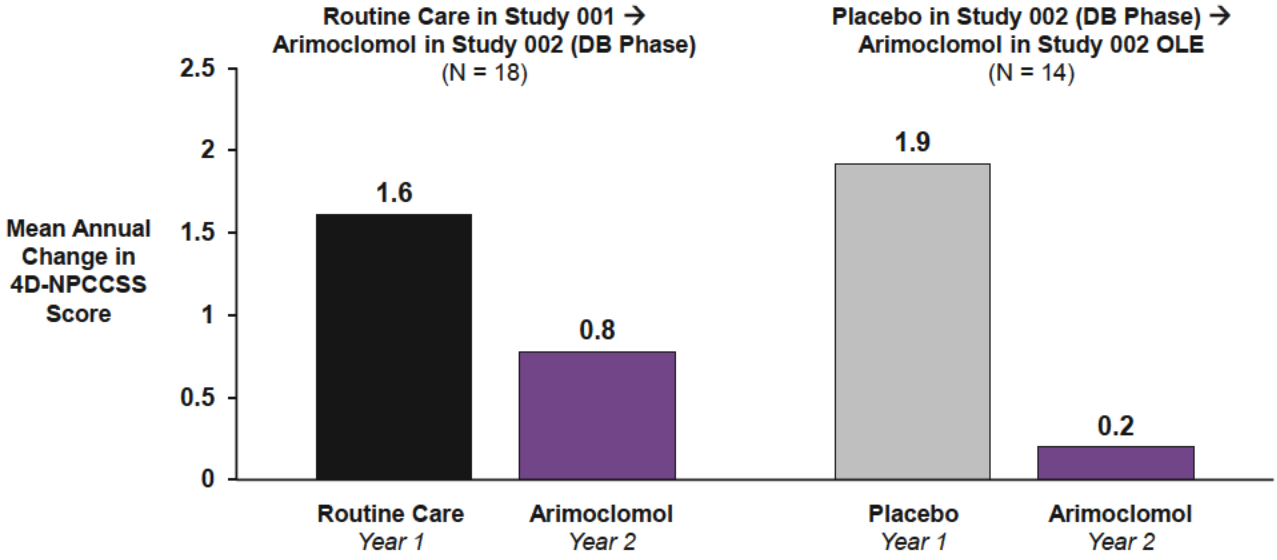
7.1.3.2 Comparison of Two Independent Crossover Cohorts

Because most patients in Study 002 were rolled over from the observational Study 001, and all placebo patients who completed the double-blind phase of Study 002 continued into the OLE phase, two relevant comparisons of the annual rates of change in disease progression as measured with the 4D-NPCCSS could be made between no treatment/placebo and arimoclomol treatment:

- Patients randomized to arimoclomol during the Study 002 double-blind phase after completing Study 001 (routine care/observation only) had 4D-NPCCSS scores decrease from 1.6 points in Year 1 to 0.8 points in Year 2 (Figure 23, left side).
- Patients who completed one year of Study 002 OLE after one year of placebo during the double-blind phase had 4D-NPCCSS scores decrease from 1.9 points in Year 1 to 0.2 points in Year 2 (Figure 23, right side).

In all the analyses, arimoclomol consistently demonstrated a slower rate of disease progression than the untreated or placebo groups (Figure 23).

Figure 21: Summary of Disease Progression Rates for Treated vs Untreated across Clinical Development Program



Note: Higher values indicate faster disease progression.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; DB = double-blind; OLE = open-label extension.

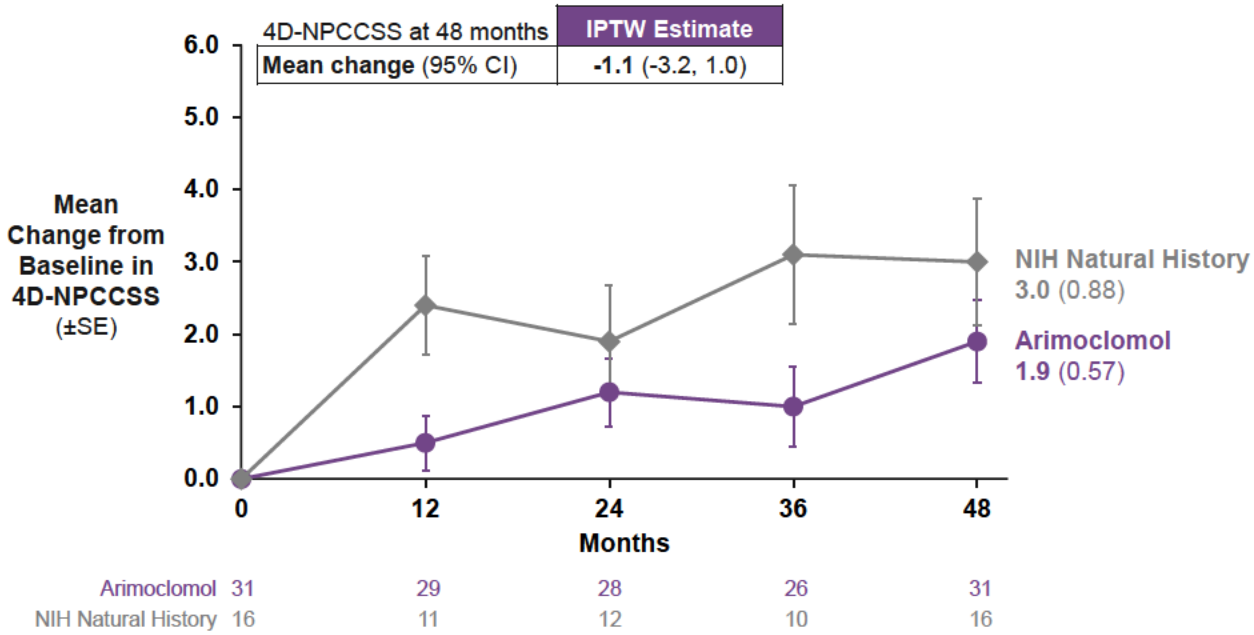
7.1.3.3 Disease Progression in NIH Natural History Cohort vs Patients Receiving Arimoclomol during Study 002 OLE

At FDA's request, Sponsor performed an analysis of 4D-NPCCSS scores from participants in the OLE phase of Study 002 with external matched controls in the NIH natural history cohort.

Patients ≥ 4 years of age at baseline treated with arimoclomol for 4 years in the OLE (N=31) progressed slower than controls from the NIH natural history cohort, as measured by change from baseline to Year 4 4D-NPCCSS score (SE): 1.9 (0.57) vs 3.0 (0.88) for arimoclomol vs NIH controls, respectively (Figure 22).

When scoring the 4D-NPCCSS for participants in the NIH cohort, the original swallow scores were used as part of the 4-domain NPCCSS endpoint used because individual scoring categories of the NPCCSS swallow domain were not reported as part of the NIH dataset. Therefore, and in order to have consistent results, the original swallow domain was also used for scoring the 4D-NPCCSS in the Study 002 OLE patients.

Figure 22: Mean Change from Baseline in 4D-NPCCSS in Patients Treated with Arimoclomol during the Open-label Extension Phase vs Matched NIH Natural History Patients



Note: the 4D-NPCCSS endpoint of both the NIH Natural History and the arimoclomol patient groups includes the original swallow domain.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; IPTW = inverse probability of treatment weighting; NIH = National Institutes of Health; SE = standard error.

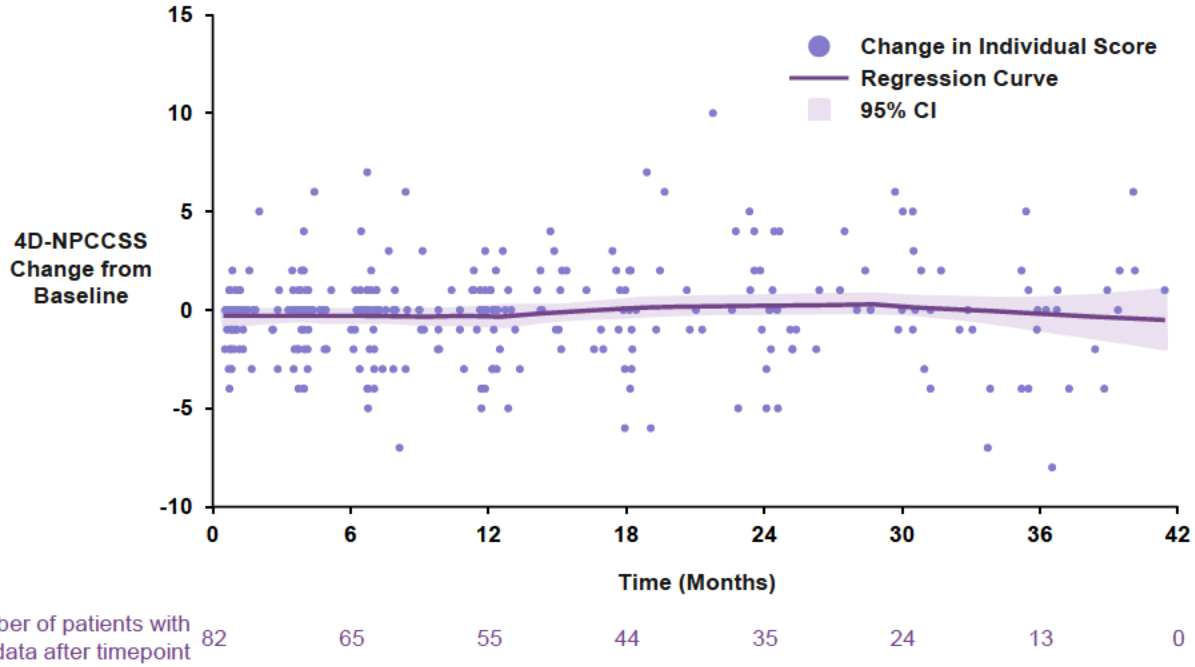
7.1.4 Expanded Access Program

Patients with NPC who did not participate in the pivotal Study 002 were eligible to receive arimoclomol through an Expanded access Program (EAP), which enrolled the first patent in 2020. As of February 2024, a total of 206 patients have received at least one dose of arimoclomol in the EAP, including 93 from the US.

Overall, EAP data indicate that the participants who received arimoclomol on average were stable for up to approximately 3.5 years with a slower disease progression as compared to untreated patients from Studies 001 (observational) and 002 (placebo).

A LOESS plot of the 4D-NPCCSS Change from Baseline is provided in Figure 23.

Figure 23: LOESS Plot of 4D-NPCCSS Change from Baseline through 42 Months in Expanded Access Program



CI = confidence interval; 4D-NPCCSS = 4-domain Niemann-Pick, type C clinical severity scale with the updated swallow domain; LOESS = locally estimated scatterplot smoothing.
Note: Patients with only baseline score or patients with no baseline score (i.e., no score prior to treatment start) were excluded. The graph shows data starting with the first assessment after treatment start up to 42 months of follow-up. The regression line is based on actual study day (in months) for each patient.

7.2 Nonclinical Confirmatory Evidence

7.2.1 In Vitro Evidence for Arimoclomol Mechanism of Action

The totality of the nonclinical data provide substantial confirmatory evidence supporting the independent and positive clinical effects of arimoclomol reported in patients with NPC. This nonclinical evidence includes mechanistic data from in vitro studies and data related to functional and objective endpoints collected in animal studies.

An overview of the in vitro studies conducted to study the MOA of arimoclomol is presented in Table 22. The in vivo studies are summarized in Section 8.2.

Table 22: Overview of In Vitro Studies Conducted with Arimoclomol

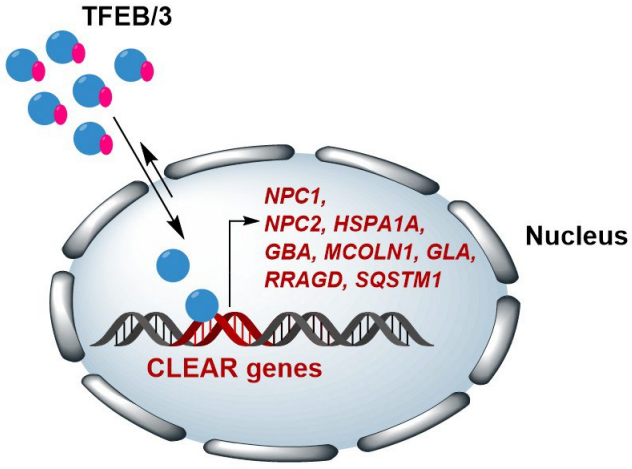
Study Title:	Cell Types and Cell Lines	Conclusions
In vitro effect of arimoclomol on TFE3 localization in human fibroblasts	NPC patients: Cell lines GM18453, GM18420, GM17912 Healthy control (WT): Cell lines GM00498, GM00969	Arimoclomol treatment of human fibroblasts from healthy controls and NPC patients led to an enhancement of nuclear translocation of the transcription factor TFE3
In vitro effect of arimoclomol on TFE3 and TFEB localization in human fibroblasts and HeLa cells under acute NPC1 inhibition	Healthy donor (WT): Cell line GM00498 HeLa cells: Clone CCL-2	Arimoclomol increased nuclear translocation of transcription factors TFEB and TFE3
In vitro effect of arimoclomol on TFE3 chromatin binding in human fibroblasts	Healthy donor (WT): Cell line GM00498	Arimoclomol enhanced binding of the transcription factor TFE3 to target gene promoters *NPC1*, *NPC2* and *GBA*
Expression of CLEAR genes in GM00498 fibroblasts with arimoclomol treatment	Healthy donor (WT): Cell line GM00498	Treatment with arimoclomol increased expression of the CLEAR network genes: *NPC1*, *NPC2*, *RRAGD*, *GBA*, *SQSTM1*, *GLA*, *MITF*, and *MCOLN1*
In vitro effect of arimoclomol and miglustat combination treatment on CLEAR gene expression in human NPC fibroblasts	NPC patient: Cell line GM18453	Arimoclomol enhanced transcription of genes from the CLEAR network alone and in the presence of miglustat
Dose-response expression of *HSPA1A*, *NPC1* and *GBA* to arimoclomol in GM18453 and GM18420 fibroblasts	NPC patients: Cell lines GM18453 and GM18420	Arimoclomol increased expression of *NPC1*, *HSPA1A* and *GBA* genes in 2 NPC patient-derived cell lines GM18453 and GM18420
In vitro proof of concept for arimoclomol in NPC patient fibroblasts	NPC patients: Cell lines GM18453, GM17911, GM17919, GM17918, GM18393, GM18390, GM18420, GM17912 Healthy control (WT): Cell lines GM00409, GM00498, GM00969	Treatment with arimoclomol led to a significant increase in total NPC1 protein. In 2 cell lines (GM18420 and GM18453), arimoclomol induced an increase of the mature form of NPC1
In vitro effect of arimoclomol on unesterified cholesterol content in human NPC fibroblasts assessed by filipin staining	NPC patient: Cell line GM18453 Healthy control (WT): Cell line GM00498	Reduction of unesterified cholesterol upon treatment of NPC patient fibroblasts with arimoclomol
In vitro effect of arimoclomol and miglustat combination treatment on unesterified cholesterol content in human NPC fibroblasts	NPC patient: Cell line GM18453 Healthy control (WT): Cell line GM00498	Reduction of unesterified cholesterol upon treatment of NPC patient fibroblasts with arimoclomol, miglustat and a combination of both

CLEAR = coordinated lysosomal expression and regulation; GBA = β-glucosylceramidase; GLA = α-galactosidase; HSPA1A = heat shock protein family A (Hsp70) member 1A; MCOLN1 = mucolipin TRP cation channel 1; MITF = melanocyte inducing transcription factor; NDA = New Drug Application; NPC = Niemann-Pick disease type C; NPC1/2 = NPC intracellular cholesterol transporter 1/2; RRAGD = Ras related GTP binding D; SQSTM1 = sequestosome 1; TFEB/E3 = transcription factor EB/E3; WT = wild type.

7.2.1.1 Effect of Arimoclomol on the Transcription Factors TFE3 and TFEB

A critical step in the MOA for arimoclomol is its involvement in the trafficking of the transcription factors TFE3 and TFEB from the cytosol to the nucleus, and their subsequent binding to various CLEAR gene promoters resulting in enhanced lysosomal and autophagic function (Figure 24). Both transcription factors, but particularly TFEB, have been identified as key components in enhancing lysosomal catabolic efficiency. An investigation of TFE3 and TFEB in healthy and NPC patient fibroblasts provided evidence that arimoclomol treatment increases the activation and translocation of these transcription factors to the nucleus and produces subsequent upregulation of the CLEAR network genes including *NPC1* and *HSPA1A* (encoding HSP70 chaperone/heat shock protein). In addition, it has been extensively reported that TFEB governs the expression of genes critical for the autophagy process including autophagy initiation, autophagosome membrane elongation, substrate capture, and autophagosomes trafficking and fusion with lysosomes (Palmieri et al., 2011; Settembre et al., 2011; Martina et al., 2014; Sardiello, 2016). Therefore, activation of TFE3/TFEB would be expected to initiate a marked increase in autophagy to support degradation of undesirable intracellular components.

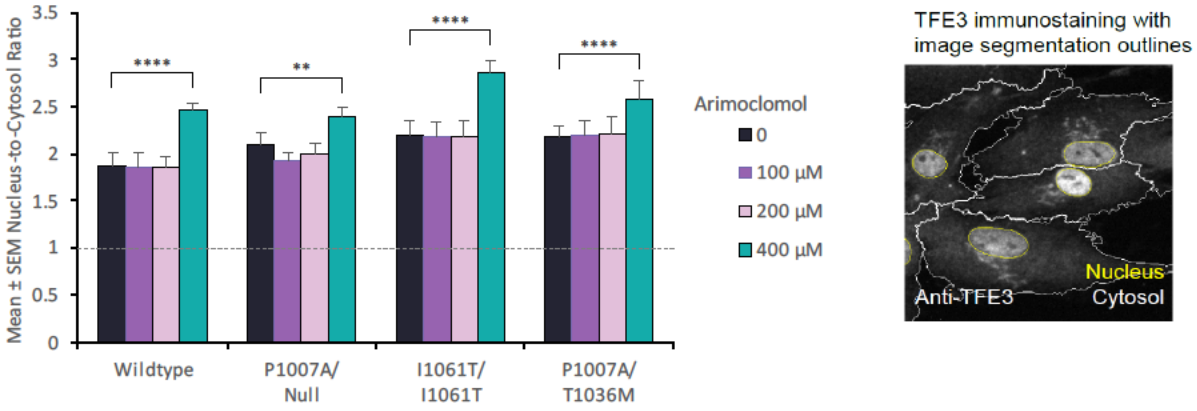
Figure 24: Arimoclomol Increased Activation of TFEB and TFE3 Upregulates Expression of CLEAR Genes Including *NPC1*



GBA = β-glucosylceramidase; GLA = α-galactosidase; MCOLN1 = mucolipin TRP cation channel 1; NPC1/2 = NPC intracellular cholesterol transporter 1/2; RRAGD = Ras related GTP binding D; SQSTM1 = sequestosome 1.

As shown in Figure 25, increased translocation of TFE3 from cytosol to the nucleus was seen with 400 µM arimoclomol in both wild-type and NPC patient fibroblasts after 1 day of treatment.

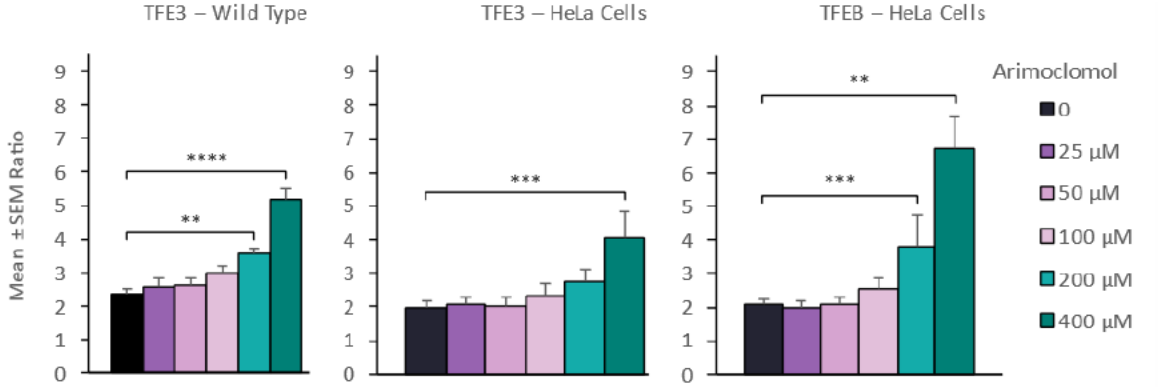
Figure 25: TFE3 Nucleus-cytosol Intensity Ratios in Healthy Human (Wild Type) and Human NPC Fibroblasts



Immunofluorescence staining of TFE3, in GM00498 (wild type), GM18420 (NPC), GM18453 (NPC), and GM17912 (NPC) fibroblasts treated with PBS (control) or 100-400 µM arimoclomol for 1 day. Experiment repeated 3 times, each column representing >2,300 total cells. Mean intensity ratio of the TFE3 staining in the nuclear to cytosolic compartments per cell was quantified and displayed as a bar graph with mean + SEM (n=3) (left) together with a magnified example image (right) with segmentation outlines of the cytosol (white lines) and nucleus (yellow lines) (right). **p<0.01; ****p<0.0001.
NPC = Niemann-Pick disease, type C; PBS = phosphate buffered saline; TFE3 = transcription factor E3.

In another study, human wild-type fibroblasts and HeLa cells were incubated with various concentrations of arimoclomol (0–400 µM) in the presence of U-18666A (0.5 µM), an NPC1 protein inhibitor that induces an NPC-like phenotype (Lu et al., 2015). Consistent with previous studies, results showed that arimoclomol enhances transport of TFE3 and TFEB (tested in HeLa cells only) from cytosol to the nucleus in a dose-dependent manner (Figure 26).

Figure 26: TFE3 or TFEB Nucleus-cytosol Intensity Ratios in Healthy Human (Wild Type) Fibroblasts and HeLa Cells Treated with Arimoclomol in Combination with NPC1 Inhibitor U-18666A



Quantifications of the nucleus-to-cytosol mean fluorescence intensity ratios of immunostainings of TFE3 in GM00498 fibroblasts, TFE3 in HeLa cells, and TFEB in HeLa cells. Cells were treated with 0-400 µM arimoclomol in combination with either vehicle or 0.5 µM NPC1 inhibitor U-18666A for 3 days. Bars depict the means of median ratios of independent experiments (n=4), each with >160 cells per sample, error bars show SEM.
NPC = Niemann-Pick disease, type C; TFE3 = transcription factor E3; TFEB = transcription factor EB.
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

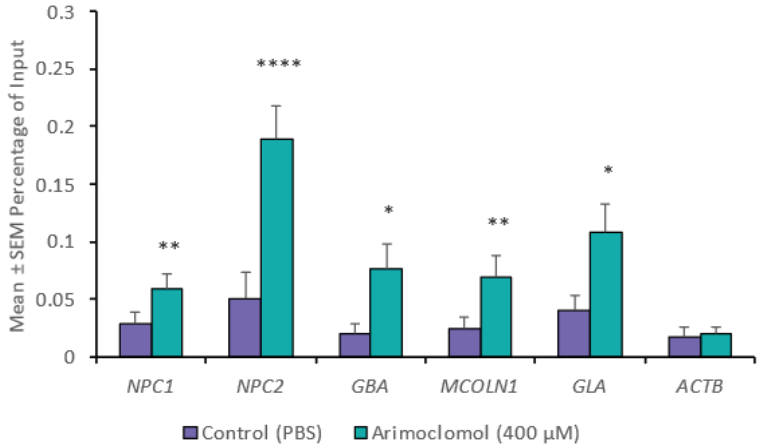
Results demonstrate a key component of both the NPC1-dependent and the NPC1-independent pathway in arimoclomol's MOA by showing how arimoclomol facilitates mobilization of transcription factors TFE3/TFEB, paving the way for upregulation of CLEAR genes, including *NPC1*.

7.2.1.2 Effects of Arimoclomol on the Expression of CLEAR Network Genes

The promoter region of the *NPC1* gene contains several elements for transcriptional regulation including CLEAR motifs (i.e., specific nucleotide sequences related to CLEAR genes). Promoter regions of lysosomal genes that contain CLEAR motifs belong to the CLEAR network (Sardiello et al., 2009; Palmieri et al., 2011). Activation of CLEAR genes has been shown to reduce lipid accumulation in several cell and animal models of lysosomal storage disorders, including NPC (Medina et al., 2011; Spampanato et al., 2013) by enhancing transcription of genes encoding lysosomal proteins that are required for lipid and glycan catabolism and export (Contreras et al., 2020). In addition, TFEB and thus, CLEAR gene activation, enhances several downstream pathways that are critical for cell health and longevity including lysosomal biogenesis, autophagy, and exo- and endocytosis (Yang et al., 2021; Sardiello et al., 2009. Palmieri et al., 2011; Zhang et al., 2020).

Another study showed that treatment with arimoclomol (400 µM) significantly enhanced the binding of TFE3 to the CLEAR promoter elements of *NPC1, NPC2, GBA, MCOLN,* and *GLA* in human wild type fibroblasts (Figure 27). This indicates that arimoclomol raises TFE3 recruitment to promoter regions of CLEAR genes resulting in increased expression of lysosomal genes including *NPC1*.

Figure 27: Enhanced Binding of TFE3 to CLEAR Elements in Target Gene Promoters after Arimoclomol Treatment

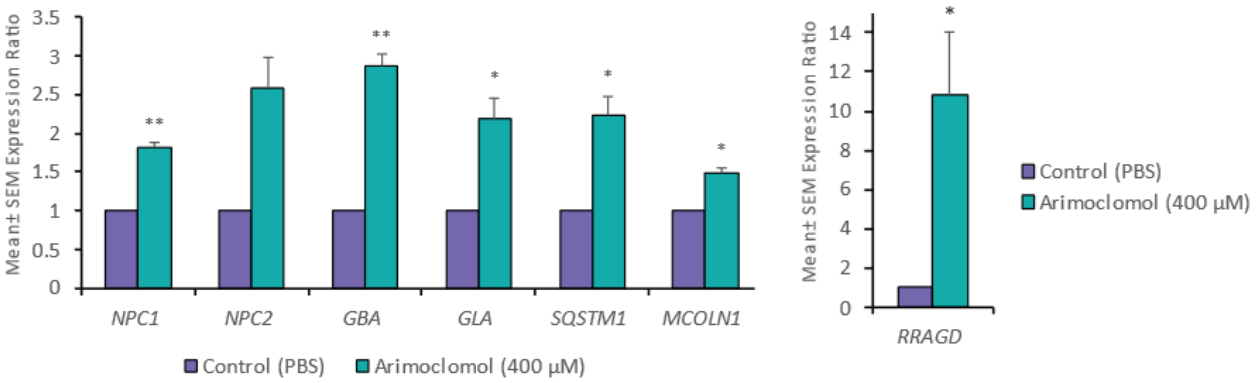


For each gene promoter, ChIP data are presented as TFE3 immunoprecipitated DNA as % of input in control (PBS) or arimoclomol (400 µM, 84–86 hours) treated healthy human fibroblasts (n = 3, mean is shown as a bar. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.
ChIP = chromatin immunoprecipitation; CLEAR = coordinated lysosomal expression and regulation; NPC = Niemann-Pick disease, type C; PBS = phosphate buffered saline; TFE3 = transcription factor E3.

Additionally, the relevant CLEAR genes related to lysosomal function (*NPC1, NPC2, GBA, GLA, MCOLN1, RRAGD, SQSTM1*) were investigated to determine whether expression of these genes was upregulated by arimoclomol in healthy human fibroblasts.

Transcriptional upregulation of all 7 tested CLEAR genes was observed with arimoclomol (400 µM) (Figure 28). The mean expression levels ranged from 1.48-fold to 10.86-fold higher vs control with most genes being expressed at approximately 2–3-fold higher rates. These results indicate that arimoclomol stimulates a CLEAR response for various genes.

Figure 28: Expression Levels of Selected CLEAR Network Genes After Treatment with 400 µM Arimoclomol in Wild Type Fibroblasts



Relative gene expression of following 5-day treatment with 400 µM arimoclomol vs control (PBS). **Left**: *NPC1*, *NPC2*, *GBA*, *GLA*, *SQSTM1*, and *MCOLN1*. **Right**: *RRAGD* (shown separately as the expression rate was markedly higher compared to the other genes). Gene quantification was performed by quantitative RT-PCR. Treatment effects were evaluated by a paired 2-tailed t-test: *p<0.05, **p<0.01.
CLEAR = coordinated lysosomal expression and regulation; GBA = β-glucosylceramidase; GLA = α-galactosidase; MCOLN1 = mucolipin TRP cation channel 1; NPC1/2 = NPC intracellular cholesterol transporter 1/2; PBS = phosphate buffered saline; RRAGD = Ras related GTP binding D; RT-PCR = reverse transcription quantitative polymerase chain reaction; SQSTM1 = sequestosome 1.

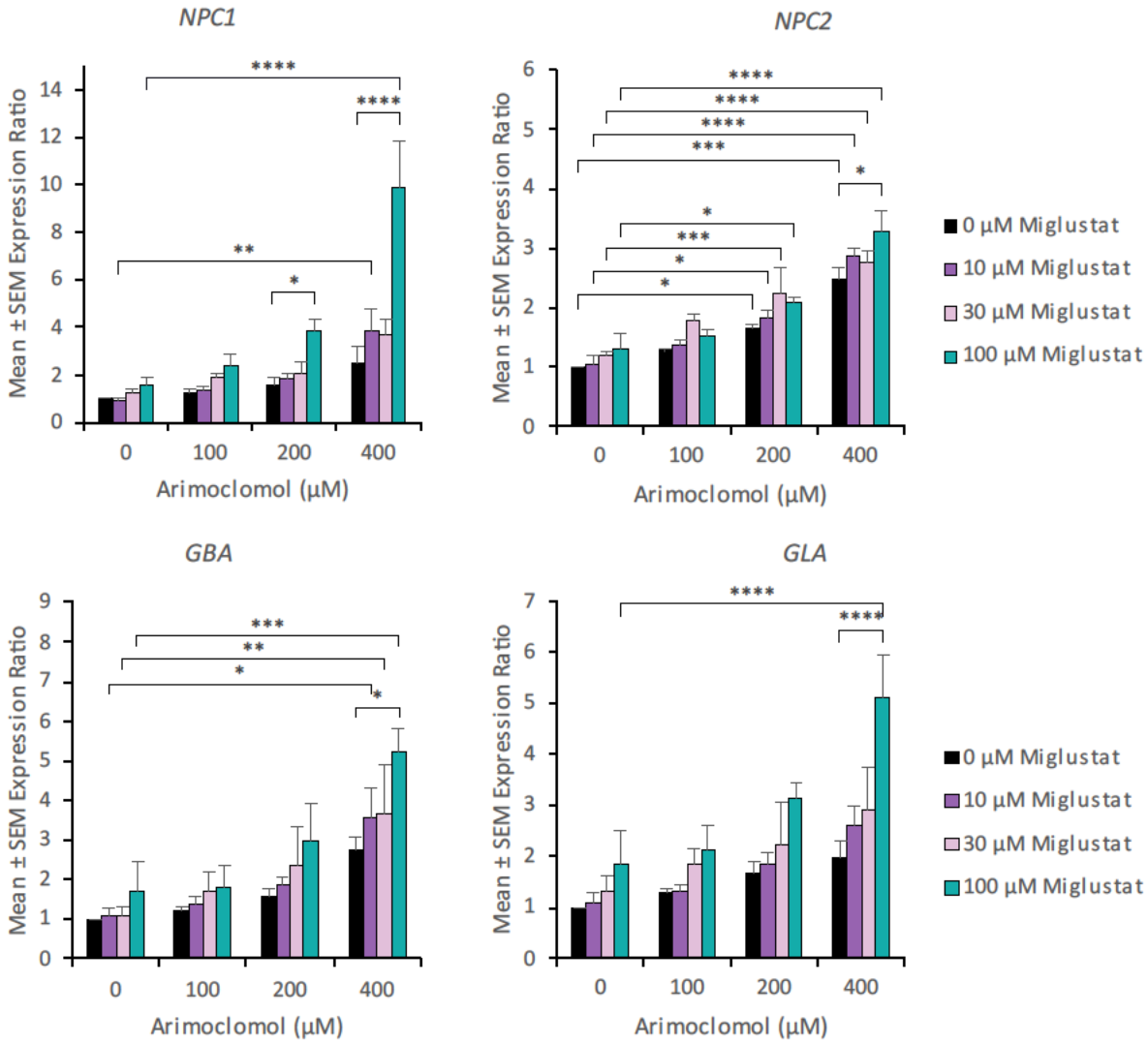
The potential for upregulation of these genes was also investigated in NPC patient fibroblasts (with ER missense mutation I1061T). In another study, seven CLEAR genes (*NPC1, NPC2, GBA, GLA, MCOLN1, RRAGD*, *SQSTM1*) and one gene involved in the heat shock and unfolded protein response, *HSPA1A* (encoding Hsp70 protein), were explored for potential upregulation by arimoclomol (0–400 µM), miglustat (0–100 µM), or by a combination of both (to assess any complementary effect). It is believed that miglustat improves lysosomal function by inhibiting glucosylceramide synthase (Ficicioglu, 2008). Most patients who participated in the clinical efficacy Study 002 also received miglustat with/without arimoclomol (26/34 in the arimoclomol group and 12/15 in the placebo group).

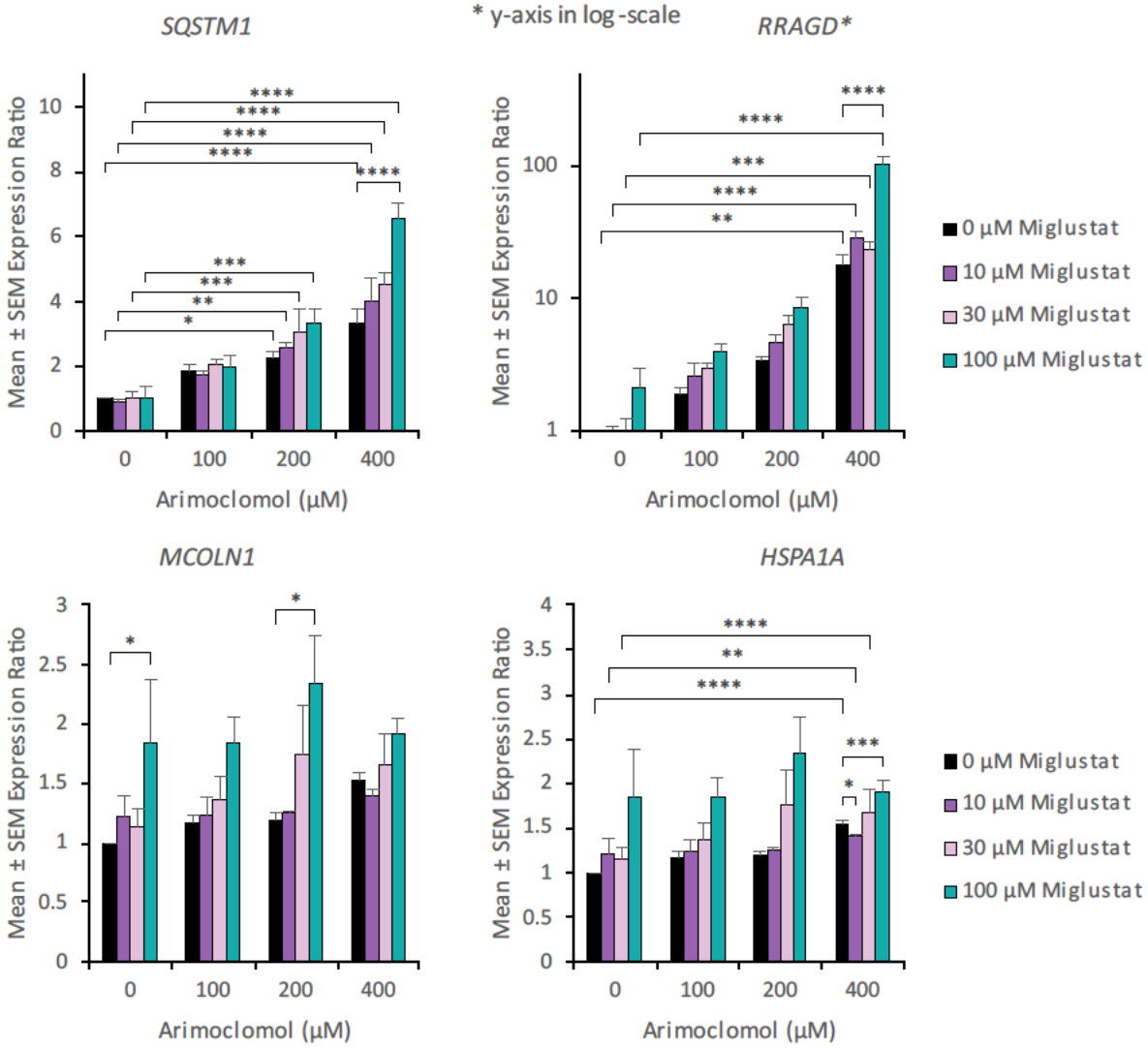
The expression rates of all 7 CLEAR genes as well as *HSPA1A* increased in a dose-dependent manner with arimoclomol alone and miglustat alone (Figure 29). When either treatment was dosed alone at 100 µM, the fold-increase in expression with either compound was comparable for *NPC1*, *NPC2*, and *RRAGD*. At 100 µM, expression rates were higher with miglustat for *GBA*, *GLA*, *MCOLN1* (encoding TRPML1, an iron channel located in endosomal/lysosomal membranes) and *HSPA1A*, and higher with arimoclomol for *SQSTM1* (encoding sequestosome-1, an autophagosome cargo protein). At concentrations > 100 µM (without miglustat), arimoclomol continued to accelerate expression levels of all 7 genes reaching statistical significance for *NPC2*, *RRAGD*, and *SQSTM1*, and *HSPA1A* at 400 µM.

Notably, a complementary effect of arimoclomol and miglustat was observed for the 7 CLEAR genes under nearly all conditions. This complementary effect reached statistical significance for

NPC1, *GLA*, *RRAGD*, and *SQSTM1* (at 400 and 100 µM for arimoclomol and miglustat, respectively), but not for *NPC2* and *GBA* when compared to arimoclomol alone. A statistically significant increase of *MCOLN1* expression over just arimoclomol was found at 200/100 µM arimoclomol/miglustat but not at 400/100 µM (Figure 29).

Figure 29: Expression Levels of Selected CLEAR Network Genes and *HSPA1A* After Treatment with Arimoclomol and Miglustat





Gene expression analysis by quantitative RT-PCR in NPC fibroblasts following 5-day treatment with 0-400 µM arimoclomol alone, or in combination with 0–100 µM miglustat, indicating fold-change of gene expression compared to vehicle-treated control. Bars represents means of 4 replicate experiments, error bars show SEM. Two-way ANOVA with Dunnett's multiple comparisons test, testing for differences between miglustat concentrations within each arimoclomol group: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. The y-axis for *RRAGD* is on a logarithmic scale.
ANOVA = analysis of variance; CLEAR = coordinated lysosomal expression and regulation; *GBA* = β-glucosylceramidase; *GLA* = α-galactosidase; *HSPA1A* = heat shock protein family A (Hsp70) member 1A; *MCOLN1* = mucolipin TRP cation channel 1; NPC = Niemann-Pick disease, type C; *NPC1/2* = NPC intracellular cholesterol transporter 1/2; *RRAGD* = Ras related GTP binding D; RT-PCR = reverse transcription polymerase chain reaction; *SQSTM1* = sequestosome 1.

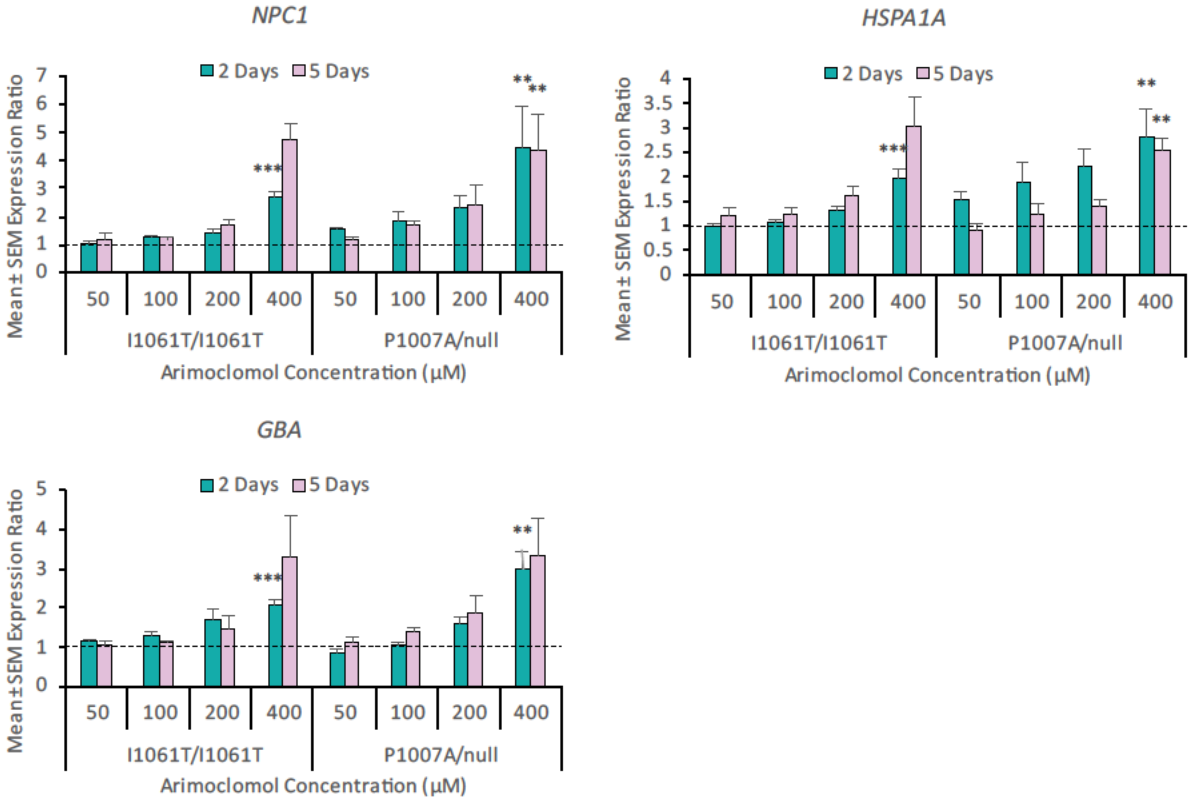
The findings of amplified expression of certain CLEAR genes and *HSPA1A* upon arimoclomol treatment were reaffirmed in a separate study assessing the effects of arimoclomol (0–400 µM) on the expression levels of *NPC1, GBA,* and *HSPA1A* in human fibroblasts with two different genotypes: I1061T/I1061T and P1007A/null mutation. I1061T is an ER missense mutation resulting in early degradation of misfolded NPC1 mutant protein that prevents its maturation and escape from the ER to the late endosomes/lysosomes. P1007A is typically associated with mild

and late onset NPC as the NPC1 mutant appears to mostly maintain a wild type-like trafficking pattern that is sufficient to preserve some level of cholesterol clearance (Ribeiro et al., 2001; Shammas et al., 2019).

Expression of all 3 test genes was enhanced by arimoclomol after 2 or 5 days of incubation in a generally dose-dependent manner (Figure 30). After 2 and 5 days of treatment, statistically significant increases over control (PBS) were reported at 400 µM arimoclomol for all 3 genes in both cell lines except for *GBA* in fibroblasts with the ER mutations after 5 days. A statistically significant difference relative to control was also found for *HSPA1A* at 200 µM arimoclomol in I1061T/I1061T fibroblasts after 2 days.

As expected, the data confirm that the activation and translocation of TFE3 and TFEB from the cytosol to the nucleus induced by arimoclomol enhances CLEAR gene expression. These results suggest that arimoclomol can improve lysosomal function in the evaluated NPC genotypes.

Figure 30: Effect of Arimoclomol on Gene Expression of *NPC1*, *GBA*, and *HSPA1A*



Results (RT-PCR) relative to PBS-treated control. Treatment effects were evaluated by 2-way ANOVA followed by Dunnett's multiple comparison test: *p<0.05, ** p<0.01, ***p<0.001, ****p<0.0001.
ANOVA = analysis of variance; *GBA* = β-glucosylceramidase; *HSPA1A* = heat shock protein family A (Hsp70) member 1A; *NPC1* = NPC intracellular cholesterol transporter 1; PBS = phosphate buffered saline; RT-PCR = reverse transcription polymerase chain reaction.

7.2.1.3 Effects of Arimoclomol on Concentrations, Maturation, and Trafficking of NPC1 Protein

The studies described above have shown that arimoclomol can mobilize the transcription factors TFE3/TFEB and thus increase expression of CLEAR genes including *NPC1* on a transcriptional

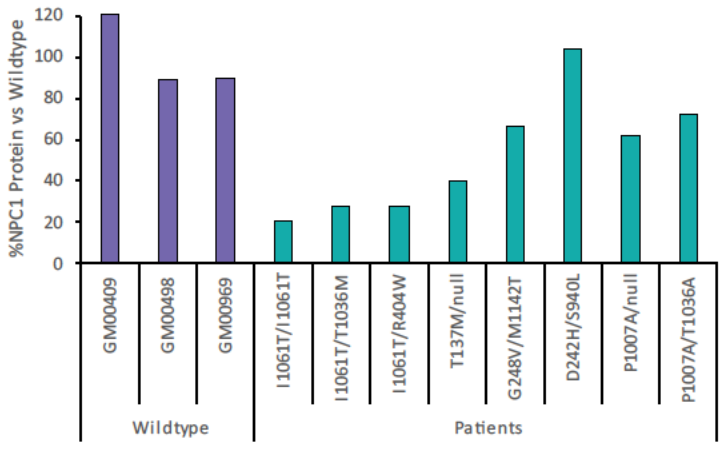
level to potentially improve lysosomal efficiency and autophagy related pathways. Based on reports by others (Shammas et al., 2019), it has been theorized that in many genotypes, particularly with ER missense mutations, overexpression of *NPC1* could increase the chance of NPC1 mutant protein being folded properly, surviving the ER quality checks, and ultimately migrating to the late endosomes to improve endolysosomal function.

To verify that arimoclomol can raise the rate of NPC1 biosynthesis and improve its maturation, another study was conducted to assess NPC1 protein levels in wild-type and NPC patient fibroblasts. Additionally, sensitivity of glycosylated NPC1 protein to endoglycosidase H (Endo H) hydrolysis was explored to determine the mobility and localization of the protein complex. Nascent membrane proteins, like NPC1, are glycosylated with mannose-rich N-glycans as they enter the lumen of the ER (Freeze and Kranz, 2010). These immature glycans can be cleaved by Endo H. However, as the protein matures during migration to the Golgi, the glycan chains are heavily processed and become resistant to Endo H hydrolysis (Gelsthorpe et al., 2008).

The NPC donor fibroblasts in this study included 3 common types of mutations that can produce functional NPC1 protein if folded properly and trafficked to the target organelles (e.g., late endosomes and lysosomes) (Shammas et al., 2019). The first type comprises ER missense mutations (e.g., the most common I1061T mutation). Mutant proteins of this type are blocked in the ER due to misfolding and early degradation. The second type consists of proteins that can reach the target late endosomes, but their transport occurs at lower rates compared to the wild type protein ("delayed"). The third type exhibits trafficking patterns similar to wild type ("WT-like") and typically results in milder phenotypes with adult-onset of disease symptoms (e.g., P1007A mutation).

At baseline, all genotypes, except for one (GM18390: D242H/S940L) showed lower NPC1 protein concentrations (21–73% of wild type) than the wild type (Figure 31). As expected, the levels of cellular NPC1 protein varied significantly depending on the genotype.

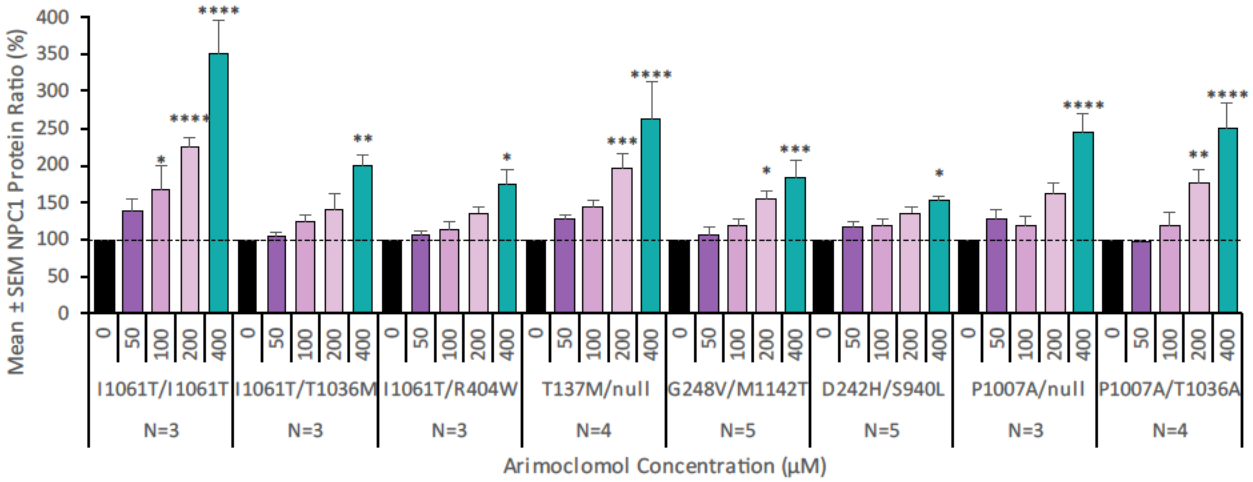
Figure 31: NPC1 Protein Concentrations in NPC Patient Fibroblast Cell Lines Relative to Wild Type



Data are presented as the percentage of the expression of each NPC patient cell line relative to the average of NPC1 protein expression of 3 different healthy donor cell lines. For each cell line, the NPC1 intensity band has been normalized to tubulin.
NPC = Niemann-Pick disease, type C; NPC1 = NPC intracellular cholesterol transporter 1.

In the second part of the study, the various fibroblasts were incubated with arimoclomol (0-400 µM). The results showed a mostly dose-dependent increase in NPC1 protein concentrations in all genotypes (Figure 32). The most pronounced effects were reported in the I1061T/I1061T (ER/ER) genotype followed by T137M/null (other/null), P1007A/T1063M (WT-like/delayed), and P1007A/null (WT-like/null). While arimoclomol increased NPC1 protein concentrations at nearly all concentrations in all genotypes in a generally dose-dependent fashion, the largest changes were found at 200 and 400 µM.

Figure 32: Effects of Arimoclomol Treatment on NPC1 Protein Concentrations in NPC Fibroblasts with Different Mutations

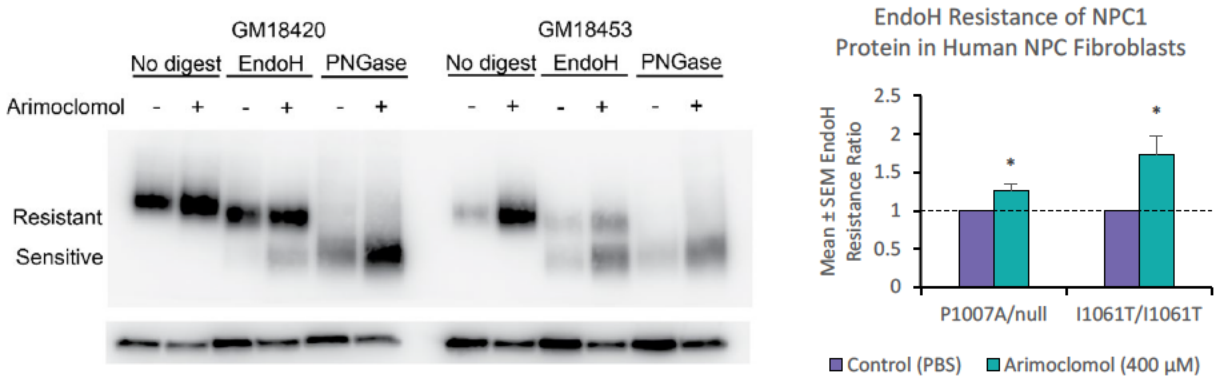


Data are presented as the mean change in % + SEM of NPC1 protein expression after arimoclomol treatment at concentrations of 50, 100, 200 and 400 µM for 5 days, relative to PBS-treated control cells from a total of 3 to 5 independent experiments, as indicated. NPC1 levels have been normalized to tubulin for GM18453 (I1061T/I1061T) and GM18420 (P1007A/null), and to ponceau staining of total protein for the other cell lines. *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001.
NPC = Niemann-Pick disease, type C; NPC1 = NPC intracellular cholesterol transporter 1; PBS = phosphate buffered saline.

To further the understanding of the possible clinical meaning of the arimoclomol induced increases in cellular NPC1 protein concentrations, arimoclomol was evaluated in Endo H assays (at 400 µM for 5 days) with fibroblasts of 2 different genotypes containing alleles of the most common mutations (ER missense I1061T and WT-like P1007A). Digestion of the glycan-protein complex (Endo H sensitive) indicates immature protein, while resistance to Endo H degradation implies maturation, escape from the ER, and transport through the cis-Golgi.

Expectedly, the increase in Endo H resistance with arimoclomol vs untreated control was higher in the genotype with the homozygous I1061T mutations (impaired ER transport) as the trafficking of $NPC1^{P1007A}$ protein is already comparable to the wild type and thus has a lower potential for improved transport.

Figure 33: Results of Endo H Assays with Arimoclomol to Assess NPC1 Protein Maturation and Localization



Left: Western blotting of extracts from NPC fibroblast cell lines harboring P1007A and a functional null allele (GM18420), or homozygous I1061T NPC1 (GM18453). PNGase cleaves all glycans from the NPC1 protein regardless of maturation status and is included as a control. Endo H sensitive, immature NPC1 is seen in PBS-treated GM18453 extracts.
Right: Quantification of the Endo H resistant NPC1, shown as arimoclomol-treated relative to untreated cells. Cells were treated for 5 days with 400 µM arimoclomol. Average of 3 independent experiments, mean ± SEM. *$p<0.05$.
Endo H = endoglycosidase H; NPC = Niemann-Pick disease, type C; NPC1 = NPC intracellular cholesterol transporter 1; PBS = phosphate buffered saline; PNGase = peptide:N-glycosidase.

Overall, the data indicate that arimoclomol does not only upregulate expression of certain CLEAR genes and specifically NPC1 at the transcriptional level, but also that this overexpression results in amplification of cellular NPC1 protein levels and more successful NPC1 processing. This allows more protein to pass through the Golgi and reach the target late endosomes/lysosomes. Increased biosynthesis would also be expected for other proteins encoded by CLEAR genes due to the upregulated expression demonstrated with arimoclomol.

A potential explanation for the enhanced trafficking of NPC1 protein could be that the increased number of synthesized protein molecules improves the odds of proper folding and escape from the ER before degradation. A second or additional explanation could be that the upregulation of *HSPA1A* expression by arimoclomol improves the function of heat shock protein 70 (Hsp70)—a mediator of the unfolded protein response and inhibitor of stress-induced cell death—to promote more efficient and successful protein folding and cell viability (Kieran et al., 2004; Kalmar et al., 2008; Neef et al., 2011; Gupya et al., 2010).

7.2.1.4 Effect of Arimoclomol on the Clearance of Unesterified Cholesterol in Human NPC Fibroblasts

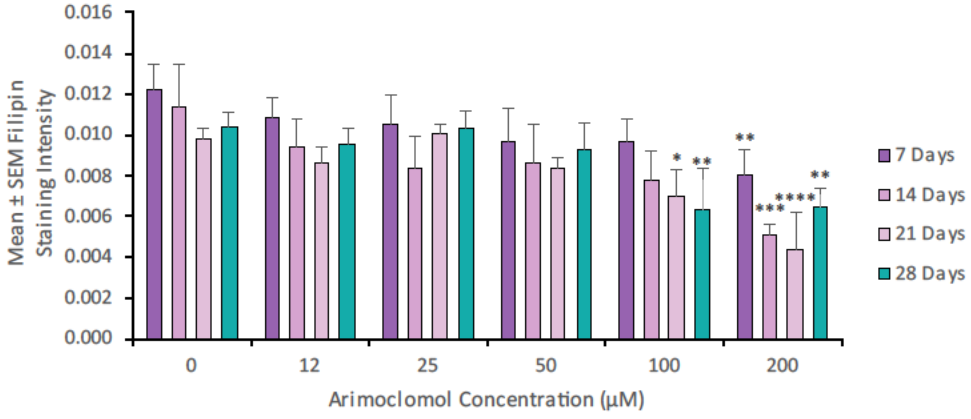
As demonstrated thus far, the arimoclomol induced activation of TFE3/TFEB results in upregulated expression of CLEAR genes including *NPC1* as well as *HSPA1A*, which encodes a protein of the heat shock family that is a critical regulator of the unfolded protein response and inhibitor of stress-induced cell death. On a cellular level, these findings suggest that arimoclomol may generally improve lysosomal function and autophagy flux to clear undesirable or toxic components from the cell. More specifically, the amplified expression response has been shown to increase cellular NPC1 protein concentrations that can improve NPC1 mutant maturation and subsequent trafficking to the late endosomes/lysosomes.

While activation of TFE3/TFEB and the resulting overexpression of CLEAR genes other than *NPC1* may already promote general cell fitness, one remaining question in the NPC1-dependent pathway is whether the demonstrated higher concentrations of mature mutant NPC1 protein can improve cholesterol clearance from the lysosome. The two in vitro studies described below were conducted to address that question.

One study was performed to determine whether arimoclomol could reduce cholesterol accumulation in the lysosomal compartment of NPC patient fibroblasts (ER/ER missense genotype with homozygous I1061T mutations) when compared to wild type fibroblasts. Unesterified cholesterol in the fibroblasts was measured through high-content imaging followed by automated image analysis of filipin staining intensity (filipin binds unesterified cholesterol).

Figure 34 illustrates the time- and dose-dependent increases in unesterified cholesterol clearance from the lysosomal compartment. Statistically significantly reduced filipin staining intensity was found following arimoclomol treatment at 200 µM at all prespecified time points (at 7, 14, 21, and 28 days) and at 21 and 28 days after treatment with 100 µM arimoclomol. Additionally, unesterified cholesterol levels decreased numerically between Day 7 and 14 and reached stable levels between Day 21 and 28. These data demonstrate that the arimoclomol-enhanced transcription processes can rescue the NPC phenotypes evaluated in this study.

Figure 34: Quantification of Unesterified Cholesterol in Lysosomal Compartment of Human NPC Fibroblasts after Arimoclomol, Measured by Filipin Staining



Plots depicting filipin intensity in the lysosomal compartment normalized by cell area in GM00498 (wild type) and GM18453 (NPC) fibroblasts treated with 0, 12, 25, 50, 100 or 200 µM arimoclomol for 7, 14, 21, or 28 days. Bars represent means of replicate experiment (n=3). Statistical analysis was performed using 2-way repeated measures ANOVA with Dunnett's multiple comparisons test: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.
ANOVA = analysis of variance; NPC = Niemann-Pick disease, type C.

Another study showed that increasing the expression of *NPC1* and other CLEAR genes with arimoclomol can activate or accelerate cholesterol clearance from lysosomal compartments. Results indicated that this overexpression can be further enhanced in the presence of miglustat. Based on these results, a follow-up study investigated the effects of combined treatment with arimoclomol (0–200 μM) and miglustat (0–100 μM) on the cholesterol clearance in NPC fibroblasts.

The design of the follow-up study was similar to its predecessor. The cell lines (I1061T/I1061T vs wild type) compared in both studies were also the same. After incubation for 7 days, a dose-dependent reduction in unesterified cholesterol in the lysosomal compartment was observed with arimoclomol alone compared to vehicle control although the percent difference in filipin staining intensities between the lowest (50 μM) and the highest (200 μM) dose was relatively modest (83% vs 79% of untreated; Table 23).

Filipin staining intensities with miglustat alone were lower at 30 μM vs 10 μM but appeared to plateau at higher concentrations even in combination with arimoclomol. Combining miglustat at 10 μM with arimoclomol also did not improve cholesterol clearance. However, complementary effects were found when miglustat concentrations were increased from 10 to 30 μM at any arimoclomol dose. Maximum reduction in unesterified cholesterol (52% of vehicle control) was reported at 200 μM arimoclomol in combination with 30 or 100 μM miglustat.

The experiments were then repeated with a longer treatment period of 14 days. As expected, the unesterified cholesterol content in the lysosomal compartment continued to decrease beyond 7 days of treatment relative to control. While the general patterns between arimoclomol/miglustat concentrations and filipin staining intensities were comparable after 7 and 14 days of treatment, the reductions in unesterified cholesterol were markedly larger after 14 days vs 7 days at most doses (Table 23; Figure 35). Together, these data indicate that the maximum effect with arimoclomol alone was achieved between 14 and 21 days in human fibroblast.

Stain intensities were comparable at 50 and 100 μM at any given miglustat dose, but a considerable reduction was found by increasing the arimoclomol concentration from 100 to 200 μM. Lysosomal cholesterol content decreased in a dose-dependent manner with miglustat from 10-100 μM. Combining arimoclomol and miglustat resulted in a substantial complementary effect. At 200 μM/100 μM arimoclomol/miglustat for 14 days, a reduction in filipin staining intensity of nearly 80% was observed compared to vehicle control. Notably, treatment for 14 days with lower dose combinations of both compounds, e.g., 50 μM/30 μM arimoclomol/miglustat, already reduced lipid burden by approximately 50%.

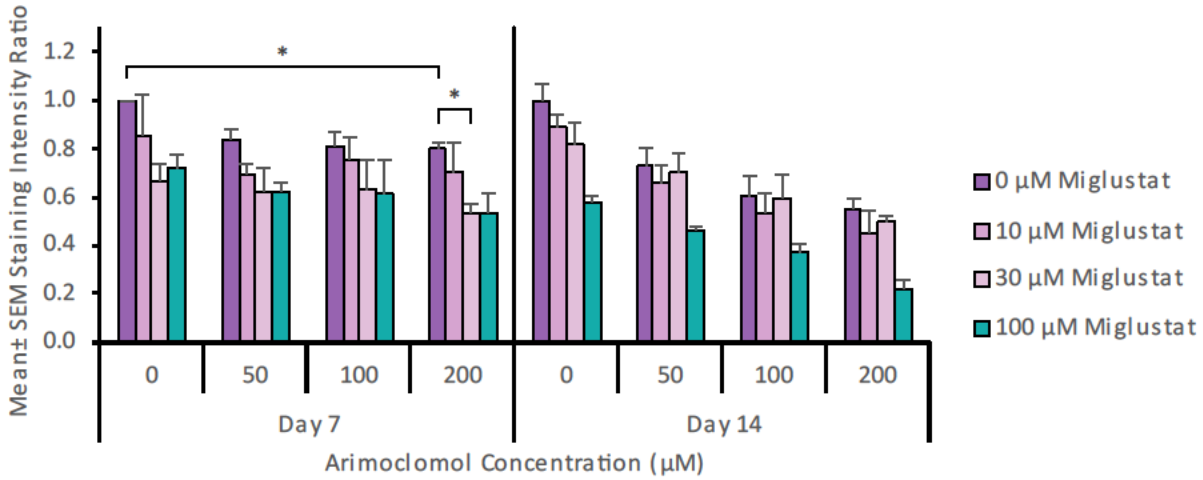
These data are consistent with reports that miglustat can decrease glycosphingolipid accumulation with downstream reduction of cholesterol in NPC fibroblasts (Patterson et al., 2007; Ficicioglu, 2008; Brogden et al., 2020). Therefore, it appears that arimoclomol and miglustat can act on independent pathways to provide complementary effects with respect to reducing lipid burden in the lysosomal compartment of NPC patients. This complementary effect of arimoclomol and miglustat was also observed in the rearing behavior and survival of *Npc1*$^{-/-}$ mutant mice, and in a slower progression rate (as measured by change in 4D-NPCCSS from baseline) in NPC patients receiving concomitant arimoclomol and miglustat when compared to the FAS in Study 002.

Table 23: Filipin Staining Intensities in the Lysosomal Compartment of Human NPC Fibroblasts as Percent of Vehicle Control After Treatment with Arimoclomol and Miglustat for 7 and 14 days

Arimoclomol Concentration (µM)	Day 7				Day 14			
	Miglustat Concentration (µM)							
	0	10	30	100	0	10	30	100
0	100%	85%	67%	72%	100%	73%	61%	56%
50	83%	69%	61%	61%	89%	65%	54%	45%
100	80%	75%	64%	61%	82%	71%	59%	50%
200	79%	70%	52%	52%	58%	46%	37%	22%

Unesterified cholesterol measured by filipin staining in NPC patient fibroblasts, as percent of vehicle-treated control. Data represents means of the medians of 2 replicate experiments with a total of > 550 cells per condition. Color ranges from highest value (white) to lowest value (green) across treatment days and arimoclomol/miglustat concentrations.
NPC = Niemann-Pick disease, type C.

Figure 35: Filipin Staining Intensity vs Control in Lysosomal Compartments of NPC (I1061T/I1061T) Human Fibroblasts Following Treatment with Arimoclomol and Miglustat for 7 and 14 Days



Filipin staining intensities in the lysosomal compartment are normalized relative to vehicle control (0 µM arimoclomol and miglustat) by Day in GM00498 (wild type) and GM18453 (I1061T/I1061T) fibroblasts treated for 7 or 14 days with 0, 50, 100, or 200 µM arimoclomol citrate in combination with 0, 10, 30, or 100 µM miglustat. 0 µM treatment indicates treatment with vehicle without drug added. Bars represent the means of replicate experiments (n = 3 and n = 2 for 7 and 14 days, respectively). Two-way repeated measures ANOVA with Geisser-Greenhouse correction and Dunnett's multiple comparisons test, grouped by either miglustat or arimoclomol, was performed for the 7-day experiments: *$p<0.05$; no statistical analysis was performed for the 14-day experiments as they were only conducted in duplicates.
ANOVA = analysis of variance; NPC = Niemann-Pick disease, type C.

7.2.1.5 Summary of In Vitro Evidence

The in vitro studies demonstrate that arimoclomol has significant effects along multiple mechanistic pathways that appear clinically relevant for NPC therapy. Prolonged activation of the transcription factors TFE3/TFEB facilitated by their translocation from the cytosol to the nucleus is a crucial step that results in upregulation of a series of downstream processes that improve lysosomal function and cell viability. The following is a summary of the key steps involved in the MOA of arimoclomol:

1. Arimoclomol initiates translocation to and/or prolongs localization of the transcription factors TFE3 and TFEB in the cell nucleus.
2. In the nucleus, TFE3 binding to CLEAR motifs is enhanced in the promoter regions of lysosomal genes (CLEAR network genes).
3. Prolonged activation and improved binding of TFE3 to CLEAR gene promoters increases CLEAR gene expression.
4. Upregulation of CLEAR gene expression raises CLEAR network protein levels including NPC1 and Hsp70 (heat shock protein and regulator of the unfolded protein response).
5. Higher concentrations of post-translational NPC1 mutant protein also increase the amount of properly folded (possibly amplified by higher levels of Hsp70) and mature protein that can escape the ER quality control and migrate through the cis-Golgi to ultimately reach the late endosomes/lysosomes.
6. Greater availability of at least partially functioning NPC1 protein (depending on genotype) in the late endosomal/lysosomal membranes results in improved clearance of unesterified cholesterol.
7. In an NPC1-independent pathway, upregulation of key CLEAR genes likely improves general cell health through heightened lysosomal efficiency and autophagy flux independent of NPC1 protein availability and functional capacity.

In conclusion, the collective in vitro data provide substantial mechanistic evidence of how arimoclomol promotes lysosomal function, autophagy flux, and clearance of unesterified cholesterol from the lysosomal compartment, thereby imparting treatment benefits in patients with NPC. Additionally, the combination of arimoclomol and miglustat demonstrated upregulation of CLEAR genes and subsequent reduction in unesterified cholesterol accumulation that was superior compared to each compound alone. Consistent with these results, subgroup analyses of the Study 002 data showed that the treatment effect of arimoclomol on the revised primary efficacy endpoint was larger in the miglustat subgroup of Study 002.

7.2.2 In Vivo Studies

Arimoclomol was investigated in six in vivo primary PD studies, five with arimoclomol alone and one with a combination of arimoclomol and miglustat. Two of these studies were previously submitted to the IND, and only study was included in the original NDA submission. The animal studies were designed to assess survival, functional capabilities, and exploratory biomarkers in two mouse models (double null *Npc1*$^{-/-}$ and homozygous *Npc1*^{nmf164} missense mutant mice). An overview of all studies is provided in Table 24. Note that all animal doses shown in this section are expressed as dose of arimoclomol citrate.

Table 24: Overview of In Vivo Primary Pharmacodynamics Studies in Mouse Models

Study Title:	Mouse Model and Strain	Dose and Route of Administration
Arimoclomol dosing study in a mouse model of Niemann-Pick Type C disease	*Npc1*$^{-/-}$ WT = BALB/c (*Npc1*$^{+/+}$) (males and females)	*Npc1*$^{-/-}$ mice received 0, 10, 30, 100, or 300 mg/kg/day arimoclomol via drinking water from age 3 weeks to termination at 7-8 weeks.
Arimoclomol dosing study in a mouse model of Niemann-Pick Type C disease	*Npc1*$^{-/-}$ WT = BALB/c (*Npc1*$^{+/+}$) (males and females)	*Npc1*$^{-/-}$ mice received 0, 10, 30, 100, or 300 mg/kg/day arimoclomol via drinking water from age 3 weeks to age 7-8 weeks (males) or humane endpoint (females). WT mice: 0 mg/kg/day.
Efficacy of a developmental compound in *Npc1* knockout mice	*Npc1*$^{-/-}$ WT = BALB/c (*Npc1*$^{+/+}$) (males and females)	*Npc1*$^{-/-}$ mice received 1, 3, 10, or 30 mg/kg/day arimoclomol via drinking water, or 10 mg/kg/twice daily by oral gavage from age 3 weeks to age 7 weeks (males) or humane endpoint (females).
A combination study of arimoclomol and miglustat in the *Npc1*^{nih} mouse model: Survival and behavior	*Npc1*$^{-/-}$ WT = BALB/c (*Npc1*$^{+/+}$) (females)	Arimoclomol only: 0 or 30 mg/kg/day via drinking water. Miglustat only: 0 or 600 mg/kg/day via food. Combination group: 30 mg/kg/day arimoclomol via drinking water + 600 mg/kg/day miglustat via food. Treated from age 3 weeks of age to humane endpoint.
Effect of arimoclomol on survival and behavior of the *Npc1*$^{nmf/nmf}$ mouse model	*Npc1*^{nmf164} WT = C57BL/6J (*Npc1*$^{+/+}$) (females)	*Npc1*^{nmf164}: 0 or 100 mg/kg/day arimoclomol via drinking water from age 3 weeks to age 12 weeks.
The effects of 100 mg/kg/day arimoclomol treatment on biochemical endpoints in the *Npc1*$^{nmf/nmf}$ mouse model	*Npc1*^{nmf164} WT = C57BL/6J (*Npc1*$^{+/+}$) (females)	*Npc1*^{nmf164}: 0, 10, 50, 100, 500 mg/kg/day arimoclomol via drinking water from age 3 weeks of age to humane endpoint

Note: All studies were non-GLP.
GLP = good laboratory practice; IND = investigational new drug; NDA = new drug application; NPC = Niemann-Pick disease, type C; Npc1 = NPC1 = NPC intracellular cholesterol transporter 1; WT = wild type.

7.2.2.1 Overview of NPC Mouse Models

Two different NPC mouse models, NPC null mutant mice (referred to as *Npc1*$^{-/-}$ or *Npc1*^{nih}) and homozygous *Npc1*^{nmf164} (or *Npc1*$^{nmf/nmf}$) missense mutant mice, were studied to potentially capture effects of arimoclomol on pathways associated with NPC1 protein biosynthesis and trafficking (*Npc1*^{nmf164} mice), and on processes that may engender treatment effects independent of NPC1 protein related pathways (*Npc1*$^{-/-}$ mice).

Npc1$^{-/-}$ mice have two functional null mutations and therefore are unable to produce any functional *Npc1* mRNA or NPC1 protein. Consequently, any observed therapeutic effects of arimoclomol in *Npc1*$^{-/-}$ mice would be due to NPC1-independent pathways. Based on the in vitro data, this key independent pathway includes upregulated CLEAR gene expression due to arimoclomol-enhanced activation of the transcription factors TFEB and TFE3 with positive downstream effects on lysosomal biogenesis and autophagy.

The *Npc1*^{nmf164} mouse model, also referred to as the Maue NPC mouse model (Maue et al., 2012), is a point mutation model of NPC with a single base pair change (A to G) in codon 1005 of *NPC1* resulting in relatively normal levels of NPC1 mRNA but substantially reduced levels of

functioning NPC1^{D1005G} protein. The NPC1^{D1005G} variant does not appear to be prone to protein misfolding and ER blockage like the human NPC1^{I1061T} variant but shares more similarities with the human NPC1^{P1007A} allele that exhibits a wild type-like trafficking pattern. Since *Npc1^{nmf164}* mice can still produce some NPC1 protein, they may represent a more relevant mouse model than *Npc1$^{-/-}$* mice with double functional null mutations that are considerably less common in humans.

In the *Npc1^{nmf164}* mouse, onset of symptoms is typically seen at approximately 9 weeks of age with a clear differentiation from wild type mice at approximately 11–13 weeks of age. Mortality of *Npc1^{nmf164}* mice is typically reported at 16 weeks of age.

Human to animal exposure ratios were estimated for the arimoclomol dosages administered in the mouse studies (Figure 36). As discussed in the subsequent sections, PD effects were found in animals at arimoclomol doses as low as 10 mg/kg/day with the most pronounced effects observed at 30–100 mg/kg/day. The arimoclomol exposure in humans at clinical doses is approximately 2 to 6 times higher compared to the exposure in mice dosed at 30–100 mg/kg/day. Therefore, the PD effects found in the animal studies are clinically relevant as they occurred at animal exposure levels that were lower when compared to arimoclomol exposure in humans.

Figure 36: Estimated Human-to-Animal Exposure Ratios in Pharmacodynamic Mouse Studies

Animal Dose (mg/kg/day)	Exposure Ratio (Human:Animal)
1	179
3	60
10	18
30	6.0
50	3.6
100	1.8
300	0.60
500	0.36

Note: Animal doses are based on arimoclomol citrate. Human PK parameters estimated from 248 mg t.i.d. arimoclomol base at steady state. Mouse PK parameters estimated from a single dose of 10 mg/kg/day arimoclomol citrate (equivalent to 6.2 mg/kg/day arimoclomol base). Exposure ratios were estimated based on C_{avg} in both species.

7.2.2.2 Survival and Functional Endpoints in Mouse Models

7.2.2.2.1 Survival

Survival was assessed in 4 of the 6 mouse PD studies: 3 in the *Npc1*$^{-/-}$ (NPC1-independent) and in one *Npc1*^{nmf164} (NPC1-dependent) mouse model. A modest but consistent positive effect on mean survival was observed with arimoclomol treatment in the dose range of 30–300 mg/kg/day across all studies (shaded cells in right column of Table 25).

Table 25: Additional Survival Time of NPC Mice Treated with Arimoclomol vs Untreated Controls

Mouse Model:	Study	Arimoclomol Dose (mg/kg/day)	Mean Survival (Days)	Additional Survival vs Control, Days (%)
Npc1$^{-/-}$	CRO-1202290013	30	86.5	8.5 (11.0)
		300	83.5	5.5 (7.1)
	CRO-1402050053	1	74.9	2.6 (3.6)
		3	71.8	-0.5 (-0.7)
		10	71.8	-0.5 (-0.7)
		30	74.5	2.3 (3.1)
		10 b.i.d.	75.5	0.5 (0.7)
		30/10 b.i.d.	75.6	2.3 (3.1)
	DOC-2110260043	30 Ari	89.0	5.6 (6.7)
		30+600 (Ari+Mig)	141	57.6 (69.0)
Npc1^{nmf164}	DOC-2201170045	10	119	1.7 (1.4)
		50	120	2.9 (2.5)
		100	128	11.0 (9.4)
		500	118	1.2 (1.0)

Ari = arimoclomol; b.i.d. = 2 times a day; Mig = miglustat; NPC = Niemann-Pick disease, type C.

Survival of *Npc1*$^{-/-}$ Mice after Treatment with Arimoclomol

While the increases in mean survival age of arimoclomol-treated *Npc1*$^{-/-}$ mice compared to untreated animals may appear small (3%–11%), simply looking at the group means does not provide the whole picture. Although mean survival rates are valuable, they can sometimes prompt inaccurate group inferences when being evaluated without the context of the individual survival distribution (especially at relatively low N values). To provide a better understanding of the overall data, the survival rates at various cut-off dates were compared across studies between untreated animals and animals treated at the same dose of arimoclomol (30 mg/kg/day in drinking water or approximately equivalent dose of 10 mg/kg/day b.i.d. via oral gavage).

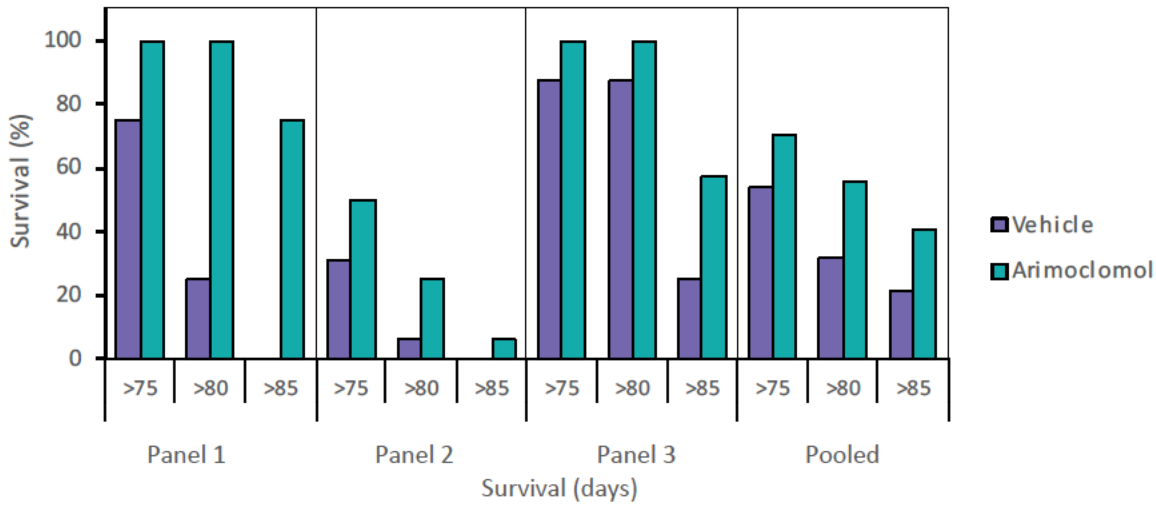
The results showed that the percentage of mice surviving longer than each 75, 80, and 85 days was always higher in the arimoclomol group vs the control group (Table 26 and Figure 37). The pooled data across the 3 studies showed that approximately 16%, 24%, and 20% more animals treated with arimoclomol (at 30 mg/kg/day or 10 mg/kg b.i.d.) survived past 75, 80, and 85 days, respectively, when compared to the untreated animals (Table 26). Overall, these data support a lengthening of survival in *Npc1*$^{-/-}$ mice treated with arimoclomol.

Table 26: Survival Rates in Female *Npc1*$^{-/-}$ Mutant Mice Treated with Arimoclomol (30 mg/kg/day) or Vehicle Control (Data Pooled Across 3 Studies)

Study Number		CRO-1202290013	CRO-1402050053	DOC-2110260043	All 3 Studies Combined
Mouse model		*Npc1*$^{-/-}$	*Npc1*$^{-/-}$	*Npc1*$^{-/-}$	
Survival Cut-Off	**Treatment**	**Number of surviving animals (n/N [%])**			
>75 days	untreated	3/4 (75%)	5/16 (31%)[a]	7/8 (88%)	15/28 (54%)
	arimoclomol	4/4 (100%)	8/16 (50%)[b]	7/7 (100%)	19/27 (70%)
>80 days	untreated	1/4 (25%)	1/16 (6%)[a]	7/8 (88%)	9/28 (32%)
	arimoclomol	4/4 (100%)	4/16 (25%)[b]	7/7 (100%)	15/27 (56%)
>85 days	untreated	0/4 (0%)	0/16 (0%)[a]	6/8 (75%)	6/28 (21%)
	arimoclomol	3/4 (75%)	1/16 (6%)[b]	7/7 (100%)	11/27 (41%)
Maximum survival (days)	untreated	81	85[a]	87	87
	arimoclomol	88	81[b]	98	98

Survival is expressed as ratio (%) of animals remaining alive (n) vs total number of animals (N) per dose group.
[a] Total of untreated animals dosed either though drinking water or oral gavage.
[b] Total of treated animals dosed either through drinking water (30 mg/kg/day) or oral gavage (10 mg/kg, b.i.d.). The gavage dose was estimated to be approximately equal to the 30 mg/kg/day drinking water group based on waste assumptions for drinking water.
b.i.d. = 2 times a day; *Npc1* = NPC intracellular cholesterol transporter 1.

Figure 37: Survival beyond 75, 80, and 85 Days in Female *Npc1*$^{-/-}$ Mice Treated with Arimoclomol (30 mg/kg/day) vs Control



Survival is expressed as ratio (%) of animals remaining alive vs total number of animals per dose group.
Results shown in Panel 1 are based on the total of untreated animals dosed either though drinking water or oral gavage and the total of treated animals dosed either through drinking water (30 mg/kg/day) or oral gavage (10 mg/kg, b.i.d.). The gavage dose was estimated to be approximately equal to the 30 mg/kg/day drinking water group based on waste assumptions for drinking water.
b.i.d. = 2 times a day; *Npc1* = NPC intracellular cholesterol transporter 1.

In summary, the general survival benefits of arimoclomol treatment in *Npc1*$^{-/-}$ mice were consistent at doses ≥ 30 mg/kg/day. It is important to interpret these results in the context of the

overall lifespan of these mutant mice with double null mutations. Treatment started at approximately 3 weeks of age with a mean survival of approximately 10–11 weeks in untreated animals. This limitation of the *Npc1*$^{-/-}$ mouse model means that treatment effects with arimoclomol can only be accrued for about 7–8 weeks to provide improvement in clinical outcome. It appears reasonable to assume that longer, chronic treatment in human patients, who progress at a much slower rate, could afford larger survival benefits regardless of genotype.

Overall, the data show that activation and amplification of the CLEAR gene network as demonstrated in the in vitro studies result in important in vivo outcomes. In *Npc1*$^{-/-}$ mice, the treatment effect is likely due to generally improved lysosomal efficiency and autophagy flux. This suggests that even genotypes with null mutations or poorly functioning NPC1 protein can benefit from arimoclomol treatment.

Survival of *Npc1*^{nmf164} Mice after Treatment with Arimoclomol

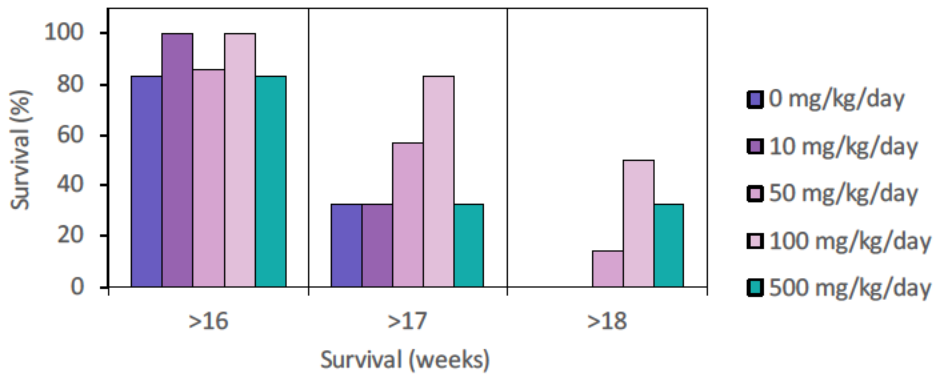
In the *Npc1*^{nmf164} mouse model, arimoclomol-treated animals demonstrated increased survival compared to the untreated group, although median survival was only statistically significantly different at 100 mg/kg/day (Table 27 and Figure 38). A higher percentage of animals in the 50 and 100 mg/kg/day arimoclomol group survived beyond 16, 17, and 18 weeks compared to the untreated group. At 500 mg/kg/day arimoclomol, 2 out of 6 (33%) *Npc1*^{nmf164} mice survived past 18 weeks, while no animal in the untreated group did.

Table 27: Survival Rates in Female *Npc1*^{nmf164} Mutant Mice Treated with Arimoclomol (10–500 mg/kg/day) or Vehicle Control

	Number of Surviving Animals (n/N [%]), by Arimoclomol Dose (mg/kg/day)				
Survival Duration, Weeks:	**0**	**10**	**50**	**100**	**500**
> 16	5/6 (83%)	6/6 (100%)	6/7 (86%)	6/6 (100%)	5/6 (83%)
> 17	2/6 (33%)	2/6 (33%)	4/7 (57%)	5/6 (83%)	2/6 (33%)
> 18	0/6 (0%)	0/6 (0%)	1/7 (14%)	3/6 (50%)	2/6 (33%)
Median survival	16.7	16.9	17.3	18.3*	16.7
Maximum survival	17.7	17.6	18.1	19.6	18.3

Survival is expressed as ratio (%) of animals remaining alive (n) vs total number of animals (N) per dose group.
Statistical significance as determined by comparison of untreated vs treated: *$p < 0.01$.

Figure 38: Survival Beyond 16, 17, and 18 Weeks of Age in Female *Npc1*^{nmf164} Mice Treated with Arimoclomol



Survival is expressed as ratio (%) of animals remaining alive vs total number of animals per dose group.

Overall, the results showed a survival benefit in animals treated with arimoclomol. At 100 mg/kg/day arimoclomol, the median survival increased by more than 11 days or approximately 10% of the total lifespan when compared to the untreated group. It was also found that *Npc1*^{nmf164} mutant mice lived longer compared to *Npc1*$^{-/-}$ mice as expected.

Survival of *Npc1*$^{-/-}$ Mice after Treatment with Arimoclomol and Miglustat

In this study, the effects of arimoclomol (at 30 mg/kg/day), miglustat (at 600 mg/kg/day), and the combination of arimoclomol and miglustat (at 30/600 mg/kg/day) were evaluated in *Npc1*$^{-/-}$ mice and compared to wild type mice and untreated *Npc1*$^{-/-}$ mice.

Miglustat alone demonstrated a larger improvement in median survival than arimoclomol alone (120 vs 90 days for miglustat and arimoclomol, respectively). It should be noted, however, that the miglustat dose was very high (a nearly 2–4 g human equivalent dose in a child or adolescent compared to a typical clinical dose of 100–300 mg miglustat) relative to the arimoclomol dose. Based on the available data, it is therefore difficult to compare the effects of arimoclomol and miglustat and make any inferences regarding survival without knowing the precise dose-response curves for either compound.

When both arimoclomol and miglustat were administered concomitantly, the survival benefit was more than additive (Table 28). Arimoclomol alone and miglustat alone increased median survival by 5.5 and 35.5 days, respectively, when compared to untreated animals. Concomitantly administered arimoclomol and miglustat lengthened survival by 57.5 days. This represents more than 2 weeks (16.5 days) of additional survival time compared to the combined individual increases for both compounds.

All comparisons of arimoclomol ($p=0.0205$), miglustat ($p<0.0001$), and arimoclomol with miglustat ($p<0.0001$) showed statistically significant increases in median survival compared to untreated mice (Table 28).

Table 28: Survival Rates in Female *Npc1*$^{-/-}$ Mutant Mice Treated with Arimoclomol, Miglustat, or a Combination of Arimoclomol and Miglustat

	Npc1$^{-/-}$ untreated	*Npc1*$^{-/-}$ arimoclomol	*Npc1*$^{-/-}$ miglustat	*Npc1*$^{-/-}$ arimoclomol/ miglustat
Dose (mg/kg/day):	**0**	**30**	**600**	**30/600**
Dose (µmol/kg/day)	0	58.8	2,740	58.8/2740
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 arimoclomol/miglustat	<0.0001	<0.0001	0.0007	-

Treatment effect was evaluated by survival curve comparisons using the Log-rank (Mantel-Cox) test.

7.2.2.2.2 Functional (Rearing)

Rearing is a functional behavior in rodents that plays an important role in exploring and interacting with the environment. As such, rearing is a complex behavior that involves aspects such as locomotion, balance, exploratory drive, spatial awareness, cognitive mapping, sequence learning, and decision making. Therefore, the ability to rear is not simply an indicator of muscle function but a broader marker of brain health in rodents. The same brain regions (particularly the cerebellum, hippocampus, and midbrain) that are responsible for controlling rearing behavior in

rodents are involved in recruiting muscles during movements related to fine motor function and swallow in humans. Rearing activity in NPC mice is therefore an appropriate indicator of neuronal health in brain regions relevant to functional endpoints like the fine motor skills and swallow domains of the NPCCSS in human NPC patients.

Across five studies, arimoclomol-treated NPC mutant mice (*Npc1*$^{-/-}$ and *Npc1*^{nmf164}) consistently outperformed the untreated controls with respect to rearing activity (particularly side rearing events). While the differences between the arimoclomol groups and the untreated groups were typically not statistically significant due to the relatively small numbers of animals and large interindividual variability, the mean differences showed clear overall trends. In 4 of the 5 studies, side or total rearing activity remained comparable to wild type for a longer time in arimoclomol-treated vs untreated mice. Moreover, in all 4 studies in which center rearing was assessed, mutant mice treated with arimoclomol retained some center rearing activity at later time points relative to untreated mice.

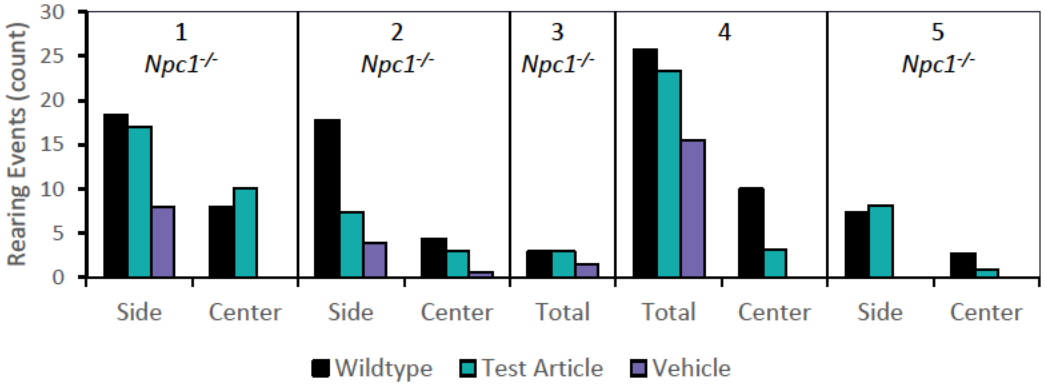
A cross-study summary of the rearing activity at comparable time points and arimoclomol doses is provided in Table 29 and Figure 39.

Table 29: Rearing Activities in Wild-Type Mice and Untreated, Arimoclomol, or Arimoclomol/Miglustat-Treated NPC Mice

Rearing Count, n:	**Arimoclomol 30 mg/kg/day**			**Arimoclomol 100 mg/kg/day**	**Arimoclomol/miglustat 30/600 mg/kg/day**
Mouse model	*Npc1*$^{-/-}$	*Npc1*$^{-/-}$	*Npc1*$^{-/-}$	*Npc1*^{nmf164}	*Npc1*$^{-/-}$
Study week	8	7	9	11	10
Wild-type	Side: 18.4	Side: 17.8	Total: 2.9	Total: 25.8	Side: 7.3
	Center: 8.0	Center: 4.4		Center: 10.0	Center: 2.7
Untreated control	Side: 8.0	Side: 3.9	Total: 1.4	Total: 15.5	Side: 0.0
	Center: 0.0	Center: 0.6		Center: 0.0	Center: 0.0
Test article	Side: 17.0	Side: 7.4	Total: 2.9	Total: 23.3	Side: 8.2
	Center: 10.0	Center: 2.9		Center: 3.2	Center: 0.8

Table represents numerical trends and not statistical analysis.

Figure 39: Rearing Activities in Wild-type Mice and Untreated, Arimoclomol, or Arimoclomol/Miglustat-Treated NPC Mice



Test article was 30 mg/kg/day arimoclomol in panels 1, 2, and 3; 100 mg/kg/day arimoclomol in panel 4; and 30/600 mg/kg/day arimoclomol/miglustat panel 5.

Rearing activity in NPC mutant mice was typically higher at doses ≥ 10 mg/kg/day arimoclomol with the largest treatment effects observed between 30 and 100 mg/kg/day when compared to untreated control animals. Differences between arimoclomol-treated and untreated animals were more pronounced near the end of the studies as disease progression resulted in more noticeable effects on rearing behavior in the untreated control group and mice in the arimoclomol groups had been treated for a longer period of time. While the rearing frequency in arimoclomol-treated mice still decreased over time, the combined data across the in vivo studies showed that this decline was slower in *Npc1*$^{-/-}$ and *Npc1*^{nmf164} mutant mice treated with arimoclomol compared to the vehicle control groups.

A combination treatment of 30 mg/kg/day arimoclomol and 600 mg/kg/day miglustat showed increased rearing events and longer preservation of rearing ability when compared to untreated *Npc1*$^{-/-}$ mice. The combination also outperformed animals treated only with miglustat and only with arimoclomol. This complementary effect related to rearing behavior is consistent with the results from multiple in vitro studies that demonstrated complementary treatment effects of arimoclomol in combination with miglustat with respect to the upregulation of CLEAR genes and reduction in cholesterol accumulation. This finding is also congruent with the increased survival observed in *Npc1*$^{-/-}$ mice, and ultimately the increased treatment effect found in the miglustat subgroup of NPC patients in clinical Study 002.

7.2.2.3 Exploratory Biomarker Investigation: Glycosphingolipid and Cholesterol Levels in Liver and Brain of *Npc1*$^{-/-}$ and *Npc1*^{nmf164} Mice

While there are no established biomarkers in humans that are proven to reliably track and correlate with NPC progression or treatment-related improvements, animal models provide the opportunity to investigate tissues and organs that are difficult or impossible to evaluate in humans (e.g., brain). Therefore, exploratory biomarkers were assessed in several in vivo studies to 1) potentially confirm certain results of the in vitro studies (e.g., upregulation of NPC1 genes in the brain), and 2) improve the understanding of the effects imparted by arimoclomol.

Levels of almost all tested glycosphingolipids (GSLs) were numerically lower in the liver and brain of *Npc1*^{nmf164} mice treated with 100 mg/kg/day arimoclomol compared to untreated mutant mice (Table 30). Statistically significant differences in the liver were seen for GM2gc, GA2, GM1, and GD1b. The decreases of GSLs in the brain were not statistically significant.

Table 30: Glycosphingolipid Levels Changes in *Npc1*^{nmf164} Mice at Age ~12 Weeks after Treatment with Arimoclomol vs Untreated

	Liver Glycosphingolipid		Brain Glycosphingolipid	
12-week Change, pmol glycan/mg protein:	Arimoclomol 100 mg/kg/day	Untreated	Arimoclomol 100 mg/kg/day	Untreated
GA2	↓ 587	↑ 820	↓ 346	↑ 416
Gb3	↓ 74	↑ 93	↓ 52	↑ 65
GD1a	↓ 78	↑ 96	↓ 2,510	↑ 2,859
GD1b	↓ 17	↑ 77	↓ 552	↑ 656
GlcCer	↓ 107	↑ 110	↑ 70	↓ 41
GM1	↓ 76	↑ 117	↓ 1,903	↑ 2,421
GM2	↓ 283	↑ 422	↓ 1,454	↑ 1,964
GM3	↓ 560	↑ 688	↓ 914	↑ 1,290
GM2gc	↓ 7,926	↑ 11,051	-	-
GM3gc	↓ 2,829	↑ 3,761	↓ 161	↑ 184
GT1b	-	-	↓ 874	↑ 952
LacCer	↓ 3,832	↑ 4,155	↓ 5,919	↑ 7,040

Arrows indicate higher or lower mean values between untreated and arimoclomol-treated groups for each glycosphingolipid.

Table 31: Statistical Analysis of Liver Glycosphingolipid Levels in Wild-type, Untreated, and Arimoclomol-treated *Npc1*^{nmf164} Mice at Age ~12 Weeks

	Untreated		Arimoclomol 100 mg/kg/day	
12-week Change, pmol glycan/mg protein:	Wild Type	*Npc1*^{nmf164}	*Npc1*^{nmf164}	p-value*
GM2gc	2,679	11,051	7,926	0.025
GA2	17.5	820	587	0.0018
GM1	0	118	76	0.001
GD1b	0	77	17	0.0003

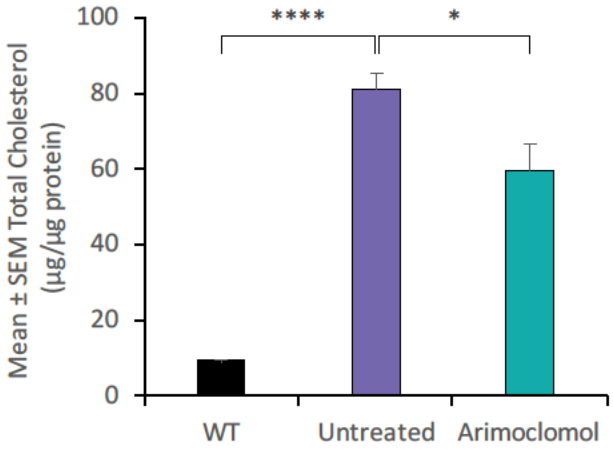
* Comparing treated to untreated values.
Only glycosphingolipids with statistically significant differences vs untreated are shown.

Unesterified cholesterol levels were assessed in the liver of *Npc1*$^{-/-}$ mutant mice 7 weeks of age. A small decrease in unesterified cholesterol was observed at 30 mg/kg/day arimoclomol but not at 300 mg/kg/day arimoclomol compared to untreated mice.

Total liver cholesterol levels in wild type mice ($p<0.0001$) and in *Npc1*^{nmf164} mice treated with 100 mg/kg/day arimoclomol ($p=0.0163$) were statistically significantly lower compared untreated *Npc1*^{nmf164} mice (Figure 40). The treatment effect in this study was likely more pronounced relative to previous studies because in *Npc1*^{nmf164} mice, arimoclomol can engender benefits not only via NPC1-independent pathways, but also by improving maturation and trafficking of the mutant NPC1 protein. Additionally, the cholesterol levels were evaluated in mice 12 weeks of age vs mice 7 weeks of age, providing additional time for arimoclomol to accumulate treatment effects.

There was no difference in total brain cholesterol between wild type, untreated, and arimoclomol-treated *Npc1*^{nmf164} mice. This finding is not unexpected since the brain is mostly an independent and highly regulated closed system with respect to cholesterol metabolism and homeostasis. Indeed, total cholesterol is typically not significantly increased in the NPC1-deficient brain compared to the wild type (Bi and Liao, 2010). The reason for this observation is that the deleterious effects of NPC stem from uneven distribution and not from overall excess of cholesterol in the brain. NPC causes dysfunctional trafficking of cholesterol that becomes sequestered in the cell bodies but is deficient in the axon of neurons (Karten et al., 2003).

Figure 40: Total Cholesterol Levels in the Liver of Wild Type, Untreated, and Arimoclomol-treated *Npc1*^{nmf164} Mice



Total cholesterol in brain. Group differences were evaluated by 1-way ANOVA followed by Dunnett's multiple comparisons test: *$p < 0.05$; **** $p < 0.0001$.
ANOVA = analysis of variance; *Npc1* = NPC intracellular cholesterol transporter 1; WT = wild type.

Generally, it is difficult to compare total cholesterol or unesterified cholesterol levels between different cell types that have naturally varying exposure to cholesterol and different functions related to cholesterol metabolism and trafficking. For example, as discussed above, the metabolism of cholesterol in the brain is mostly independent from the systemic circulation and other tissues. The liver, however, is a large throughput organ exposed to an open system of cholesterol transport as well as cholesterol from food. A key function of the liver is to regulate overall body levels of cholesterol. It synthesizes approximately 50% of all systemic cholesterol (Shi et al., 2022). This may enable the liver to accumulate more cholesterol than the brain and

may be a reason why total cholesterol was significantly higher in the liver but not in the brain of NPC mice compared to wild type and arimoclomol-treated mice.

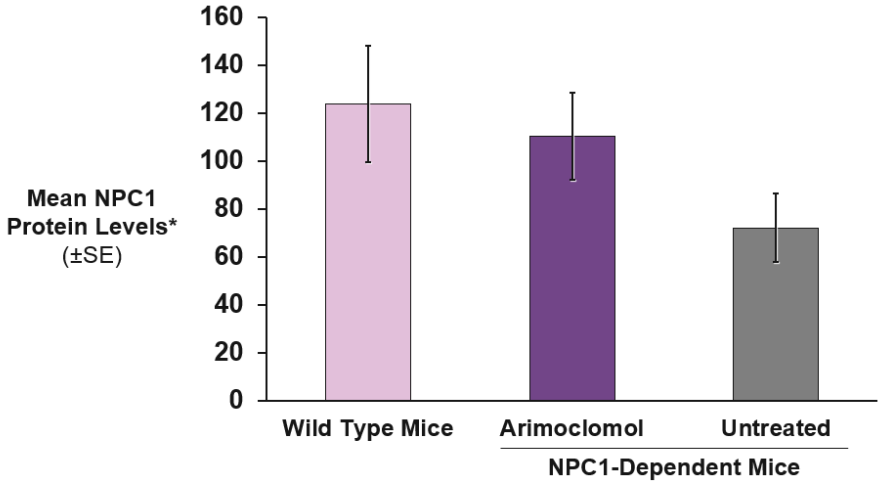
7.2.2.4 Biomarker Investigation: NPC1 Protein Concentrations in Brain and Liver of *Npc1^{nmf164}* Mice

Analysis of NPC1 protein concentrations in the brain of wild type and *Npc1^{nmf164}* mice showed the presence of 2 different isomers of NPC1. Isoform 1 (> 250 kDa) appeared to be a protein dimer (2 protein units) while isoform 2 (~150 kDa) was assumed to be a monomer (1 protein unit) of NPC1.

The NPC1 dimer is a more complex, mature, and highly glycosylated form of NPC1 that unlike the monomer was resistant to endoglycosidase (Endo) H degradation (Endo H resistance indicates that the newly formed protein has moved out of the ER into the Golgi complex) (Brogden et al., 2020). This dimer seemed to be more thermodynamically stable and trafficking competent than the monomer. Consequently, this isoform of NPC1 was able to migrate out of the ER to the late endosomes.

The data indicated a numerically higher mean concentration of the dimeric isoform 1 of NPC1 protein in the brain of mutant mice treated with arimoclomol at 100 mg/kg/day vs untreated animals (Figure 41). Moreover, the isoform 1 levels in the arimoclomol group were comparable to concentrations found in brain of the wild type mice.

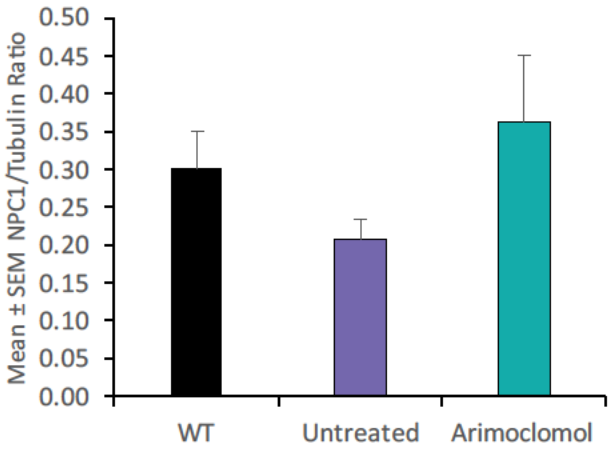
Figure 41: Concentrations of Mature Isoform 1 of NPC1 Protein in Brains of Wild-type, Untreated, and Arimoclomol-treated NPC dependent (*Npc1^{nmf164}*) Mouse



* NPC1 protein levels (isoform 1: >250 kDa and isoform 2: ~150 kDa) are normalized to tubulin.
Note: NPC1-dependent mice (*Npc1^{nmf164}*) have a D1005G point mutation.
NPC1 = NPC intracellular cholesterol transporter 1.

NPC1 protein levels were highly variable in the liver of *Npc1*^{nmf164} mice treated with arimoclomol at 100 mg/kg/day. While mean concentrations were numerically higher in the arimoclomol group compared to untreated, and the wild-type group (mean NPC1-to-tubulin ratio of 0.36, 0.21 and 0.30, respectively), this difference was not statistically significant (Figure 42).

Figure 42: Liver Concentrations of NPC1 Protein in Wild-type, Untreated, and Arimoclomol-treated *Npc1*^{nmf164} Mice



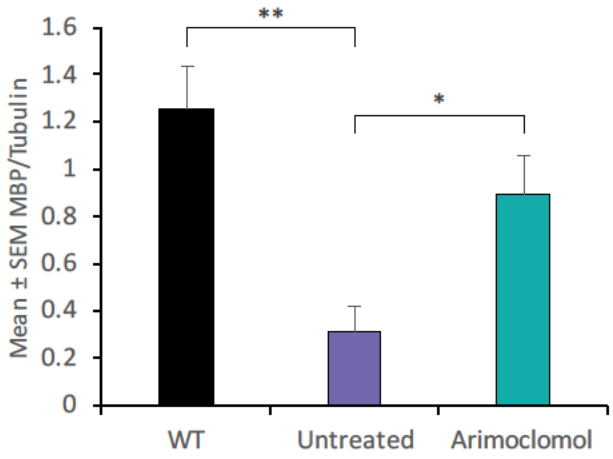
NPC1 protein levels are normalized to tubulin. Group differences were evaluated by 1-way ANOVA followed by Dunnett's multiple comparisons test.
ANOVA = analysis of variance; *Npc1* = NPC intracellular cholesterol transporter 1; WT = wild type.

7.2.2.5 Biomarker Investigation: Myelin Basic Protein Concentrations in Brain of *Npc1*^{nmf164} Mice

As mentioned above, cholesterol plays an important role in the membranes of brain cells. Approximately 80% of the brain cholesterol can be found in myelin that forms a protective sheath around neuronal axons to provide electrical insulation (Bernardo et al., 2021). Another important component of myelin is MBP that interacts with cholesterol to maintain its structural integrity (Deber and Reynolds, 1991). There is evidence that NPC results in myelination defects that lead to neuronal degradation. Decreased expression of MBP has been reported in the *Npc1*^{nmf164} mouse model which can lead to hypomyelination (Muller et al., 2013; Bernardo et al., 2021).

Concentrations of MBP were statistically significantly higher in the brain of *Npc1*^{nmf164} mutant mice treated with arimoclomol at 100 mg/kg/day compared to untreated mice (Figure 43). The increased brain levels of MBP in *Npc1*^{nmf164} mice suggest a slowing effect of arimoclomol on demyelination that could improve neuronal health. Overall, it adds to the body of evidence that arimoclomol can slow disease progression and provide a degree of phenotype stabilization.

Figure 43: Brain Concentrations of Myelin Basic Protein in Wild-type, Untreated, and Arimoclomol-treated *Npc1*^{nmf164} Mice



Bar graph of mean ± SEM MBP levels normalized to tubulin. Group differences were evaluated by 1-way ANOVA followed by Dunnett's multiple comparisons test (*p<0.05, **p<0.01).
ANOVA = analysis of variance; MBP = myelin basic protein; WT = wild type.

7.2.2.6 Summary of In Vivo Evidence

Overall, the data generated in the 6 in vivo PD studies show a beneficial effect of arimoclomol on survival. Among the functional endpoints, rearing activity was most consistently improved or maintained in arimoclomol-treated mutant mice when compared to vehicle control animals. Notably, rearing frequency in NPC mutant mice is likely a direct indicator of neuronal health of the cerebellum, hippocampus, and midbrain that are involved in governing fine motor movements including swallowing and chewing in humans. Therefore, the consistent results of improved rearing function across multiple studies and in 2 mouse models provide confirmatory evidence of effectiveness in support of the treatment benefits found in fine motor skills and swallow function in NPC patients treated with arimoclomol vs placebo (Study 002).

With respect to exploratory biomarkers, arimoclomol reduced total cholesterol levels and certain GSLs in the liver of *Npc1*^{nmf164} mice compared to untreated animals. Notably, the concentration of a mature and trafficking competent isoform of NPC1 protein was numerically elevated in the brain of *Npc1*^{nmf164} mice treated with arimoclomol. Statistically significantly increased levels of MBP in the brain of *Npc1*^{nmf164} mice suggest arimoclomol may slow axonal demyelination and neuronal degradation compared to untreated animals.

Consistent with the mechanistic findings of the in vitro studies, the totality of evidence from the in vivo studies showed that arimoclomol produces treatment benefits in animals at clinically relevant doses that are predictive of therapeutic effects in NPC patients. This is consistent with the results of clinical Study 002 that demonstrated symptom stabilization and slowing of disease progression in NPC patients. The arimoclomol effect was amplified in both animals and humans when administered in combination with miglustat.

8. Clinical Safety

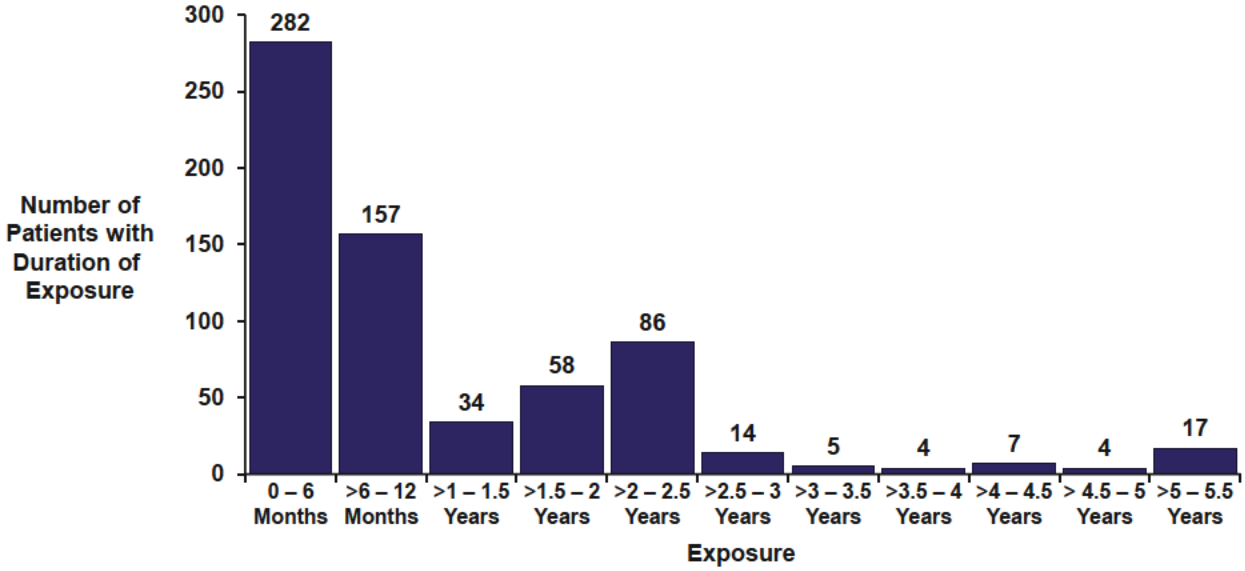
Summary

- Arimoclomol is well-tolerated with an acceptable safety profile that does not add to the high patient disease burden of NPC.
- Overall, 874 individuals have received arimoclomol, 668 individuals in clinical studies across all indications and 206 individuals in the EAP.
- The double-blind and OLE phases of Study 002 provided safety data for up to 5 years in patients with the proposed indication at the recommended dose of arimoclomol.
- The incidence of SAEs during the double-blind phase was lower in the arimoclomol group.
- Three patients in the arimoclomol group reported an AE leading to discontinuation during the double-blind phase, all of which resolved without sequelae.
- In Study 002, one death occurred during the double-blind phase in the arimoclomol group. In the 4-year OLE phase, two deaths occurred. All 3 deaths were considered related to the NPC disease and not related to treatment.
- The safety profile during the 12-month OLE phase is consistent with the double-blind phase.

8.1 Treatment Exposure

A total of 874 individuals have received ≥ 1 dose of arimoclomol across all clinical programs, including 668 participants in clinical studies and 206 patients in the EAP. The total duration of arimoclomol exposure across all completed trials totals 708.1 patient-years (Table 3) with 229 patients receiving ≥ 1 year of treatment and 137 patients receiving ≥ 2 years (Figure 44).

Figure 44: Histogram of Durations of Arimoclomol Exposures in All Completed Studies across All Indications



Note: Includes all participants receiving at least 1 dose of arimoclomol.

The primary safety dataset for patients with NPC comprises the 50 patients from the double-blind phase of Study 002 (i.e., the FAS; N=34 arimoclomol; N=16 placebo; Table 32). During the double-blind phase, most patients in both treatment groups were exposed for 26 weeks or more.

Of the 42 patients who completed the double-blind phase, 41 entered the OLE phase, during which most patients (82.9%) were exposed to arimoclomol for a total of 2.5 years or longer (Figure 45).

In addition, a total of 93 patients with NPC have received arimoclomol through an EAP in the US (additional details provided in Section 8.5).

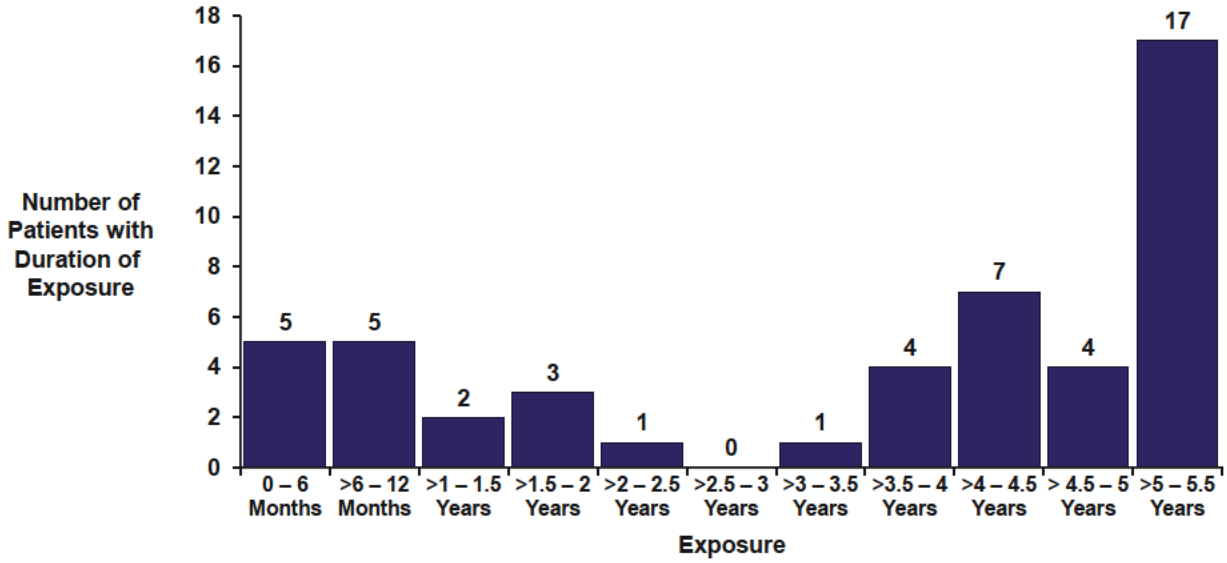
Data from Study 001 are not included because the study was observational only, and participants did not receive arimoclomol.

Table 32: Overview of Treatment Exposure in Study 002 (Double-blind and OLE Phases)

	Double-blind Phase (FAS)		Open-label Extension
Exposure:	**Arimoclomol (N=34)**	**Placebo (N=16)**	**Arimoclomol (N=41)**
Total, days	10,435	5,321	60,321
Mean, days (SD)	306.9 (107.7)	332.6 (90.1)	1,471.2 (526.1)
Min – Max	30 – 403	1 – 389	145 – 1923

FAS = Full Analysis Set; OLE = open-label extension; SD = standard deviation.
Note: Single pharmacokinetic dose not included.

Figure 45: Histogram of Durations of Arimoclomol Exposures in Study 002 (Double-blind and OLE Phases)



OLE = open-label extension

8.2 Overall Safety

During the double-blind phase of Study 002, most patients reported an AE (Table 4). Three patients in the arimoclomol group and none in the placebo group experienced AEs leading to discontinuation of study drug, all of which resolved without sequelae. One patient died in the arimoclomol group during the double-blind phase, but the event was adjudicated as not related to arimoclomol (additional details provided in Section 8.3.4).

8.3 Adverse Events during Study 002 Double-blind Phase

8.3.1 Common Adverse Events

The incidences of common AEs by preferred terms were similar between the arimoclomol and placebo groups, with the exception of upper respiratory tract infection and weight decreased, both of which occurred more frequently in the arimoclomol group compared to placebo (Table 33). Nasopharyngitis, gastroenteritis, epilepsy, ear infection, eye infection, and pneumonia all occurred more frequently in the placebo group.

Table 33: Study 002: Common Adverse Events Reported in ≥ 10% of Patients in Either Treatment Group (Double-blind Phase)

Preferred Term, n (%):	Arimoclomol (N=34)	Placebo (N=16)
Any Adverse event	30 (88.2)	12 (75.0)
Vomiting	8 (23.5)	4 (25.0)
Diarrhea	7 (20.6)	3 (18.8)
Constipation	7 (20.6)	3 (18.8)
Pyrexia	6 (17.6)	3 (18.8)
Upper respiratory tract infection	6 (17.6)	1 (6.3)
Rhinitis	5 (14.7)	2 (12.5)
Weight decreased	5 (14.7)	0
Bronchitis	4 (11.8)	2 (12.5)
Nasopharyngitis	2 (5.9)	4 (25.0)
Gastroenteritis	2 (5.9)	2 (12.5)
Epilepsy	1 (2.9)	2 (12.5)
Ear infection	0	2 (12.5)
Eye infection	0	2 (12.5)
Pneumonia	0	2 (12.5)

8.3.2 Serious Adverse Events

The proportion of patients reporting a SAE during the double-blind phase was 14.7% in the arimoclomol group and 31.3% in the placebo group (Table 34).

Most SAEs were single events and only two PTs were experienced by > 1 patient in either group (urticaria: 2 patients in the arimoclomol group; pneumonia: 2 patients in the placebo group). In both groups, the SAEs were mainly of the type that is expected in the NPC population.

Three SAEs (2 events of urticaria and 1 event of angioedema) led to discontinuation of study drug and 2 SAEs (hypophagia [in the placebo group] and epileptic encephalopathy [in the arimoclomol group]) led to interruption of treatment. The majority of SAEs resolved by the end of the double-blind phase.

Table 34: Study 002: Serious Adverse Events (Double-blind Phase)

Preferred term, n (%):	Arimoclomol (N=34)	Placebo (N=16)
Any serious adverse event	5 (14.7)	5 (31.3)
Urticaria	2 (5.9)	0
Angioedema	1 (2.9)	0
Aspiration bronchial	1 (2.9)	0
Cardio-respiratory arrest	1 (2.9)	0
Dysphagia	1 (2.9)	0
Epileptic encephalopathy	1 (2.9)	0
Malnutrition	1 (2.9)	0
Respiratory distress	1 (2.9)	0
Pneumonia	0	2 (12.5)
Diarrhea	0	1 (6.3)
Epilepsy	0	1 (6.3)
Foot deformity	0	1 (6.3)
Hypophagia	0	1 (6.3)
Laceration	0	1 (6.3)
Lower respiratory tract infection	0	1 (6.3)

8.3.3 Adverse Events Leading to Discontinuation

AEs in three patients in the arimoclomol group and no events in the placebo group led to discontinuation of study drug (Table 35). All events were moderate in severity and recovered following discontinuation of arimoclomol.

Table 35: Study 002: Adverse Events Leading to Discontinuation (Double-blind Phase)

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

8.3.4 Deaths

A total of three deaths have been reported in the completed double-blind and OLE phases of Study 002. One patient died due to cardio-respiratory arrest in the double-blind phase, and two patients died in the OLE phase, one due to lower respiratory tract infection and one due to aspiration pneumonia (Table 36). All three events were assessed as related to progression of NPC disease and not related to study drug. The last available 4D-NPCCSS score for all patients prior to death was at or near the maximum symptom severity score of 20. (Patient narratives are provided in Appendix 11.1.)

Table 36: Summary of Deaths in Study 002

Study Phase:	Age at Time of Death (Years)/Sex	SAE Leading to Death	Days of Treatment	Treatment Status	Last Available 4D-NPCCSS Score[b]	Medical History	Related to Arimoclomol
Double-blind	8/ Female	Cardio-respiratory arrest	246	On-treatment	18/20	Dysphagia, seizures, aspiration of liquids	No
OLE	13/ Female	Lower respiratory tract infection	434[a]	On-treatment	20/20	Seizures, elevated AST, scoliosis	No
OLE	19/ Male	Aspiration pneumonia	1,878[a] (5 years)	On-treatment	20/20	NR	No

a. The two participants who died during the OLE phase of Study 002 also participated in the double-blind phase.
b. Scores are presented as total score (points) out of a maximum of 20 points.
4D-NPCCSS = 4-domain Niemann-Pick disease, type C Clinical Severity Scale; AST = aspartate aminotransferase; OLE = open-label extension; NR = not reported.

8.4 Adverse Events during Study 002 Open-label Extension Phase

Most events were mild or moderate in severity (Table 5), although a higher proportion of patients reported an SAE in the OLE phase than in the arimoclomol group during the double-blind phase. However, the OLE was up to four times longer than the double-blind. As noted above, two patients died during the OLE phase due to an AE. (Narratives are provided in Appendix 11.1.2.)

8.4.1 Common Adverse Events

During the OLE phase, the most commonly reported AEs were similar to those reported in the double-blind phase of the study (Table 37).

Table 37: Study 002: Common Adverse Events Reported in ≥ 10% of Patients (Open-label Extension Phase)

Preferred Term, n (%):	Arimoclomol (N=41)
Any adverse event	38 (92.7)
Diarrhea	10 (24.4)
Upper respiratory infection	10 (24.4)
Nasopharyngitis	8 (19.5)
Epilepsy	8 (19.5)
Corona virus infection	8 (19.5)
Seizure	7 (17.1)
Cough	7 (17.1)
Bronchitis	7 (17.1)
Weight decreased	6 (14.6)
Epistaxis	6 (14.6)
Constipation	6 (14.6)
Rhinitis	5 (12.2)
Influenza	5 (12.2)
Vomiting	5 (12.2)
Gastroenteritis	5 (12.2)
Eczema	5 (12.2)

8.4.2 Serious Adverse Events

In line with progression of NPC, and as expected for a longer data collection period, the proportion of patients (N=41 receiving arimoclomol) who reported an SAE during the 4-year OLE phase was higher than patients who received arimoclomol during the 1-year double-blind phase: 15/41 (36.6%) vs 5/34 (14.7%), respectively. Most events were single events, and only four preferred-term SAEs were experienced by more than one patient (Table 38). The SAEs were mainly of the type that is expected in the NPC population.

Table 38: Study 002: Serious Adverse Events (Open-label Extension Phase)

Preferred Term, n (%):	Arimoclomol (N=41)
Any serious adverse event	15 (36.6)
Pneumonia	3 (7.3)
Urinary tract infection	2 (4.9)
Weight decreased	2 (4.9)
Epilepsy	2 (4.9)
Pneumonia aspiration	2 (4.9)
Anemia	1 (2.4)
Constipation	1 (2.4)
Diarrhea	1 (2.4)
Mouth hemorrhage	1 (2.4)
Pyrexia	1 (2.4)
Bronchitis	1 (2.4)
Gastroenteritis	1 (2.4)
Influenza	1 (2.4)
Lower respiratory tract infection	1 (2.4)
Osteomyelitis	1 (2.4)
Pharyngitis	1 (2.4)
Upper respiratory tract infection	1 (2.4)
Femoral neck fracture	1 (2.4)
Patella fracture	1 (2.4)
Oxygen saturation decreased	1 (2.4)
Decreased appetite	1 (2.4)
Feeding intolerance	1 (2.4)
Dystonia	1 (2.4)
Lethargy	1 (2.4)
Seizure	1 (2.4)
Proteinuria	1 (2.4)
Chronic respiratory failure	1 (2.4)
Pleural effusion	1 (2.4)
Tonsillar hypertrophy	1 (2.4)
Complete oral rehabilitation	1 (2.4)

8.4.3 Adverse Events Leading to Discontinuation

During the OLE phase, five AEs in four patients (9.8%) led to discontinuation of study drug (Table 39). The AEs leading to discontinuation included pneumonia aspiration, hypertonia, tremor, lower respiratory tract infection, and anxiety. One patient reported two events: hypertonia and tremor. The events of pneumonia aspiration and lower respiratory tract infection

were reported as SAEs that led to patient death, both of which were reported as related to disease progression and not related to study drug (Table 36; Section 8.3.4).

Table 39: Study 002: Adverse Events Leading to Discontinuation (Open-label Extension Phase)

AE Leading to Discontinuation:	Severity	Study Day Onset	Outcome
Pneumonia aspiration	Severe	1,484	Death
Hypertonia and tremor	Moderate	82	Resolved
Lower respiratory tract infection	Severe	36	Death
Anxiety	Moderate	978	Resolved

AE = adverse event.

8.5 Confirmatory Evidence of Safety

8.5.1 Clinical Confirmatory Evidence: Safety from Expanded Access Program

An EAP for patients with NPC was initiated by the Sponsor and the first patent was enrolled in July 2020. As of 01 February 2024, a total of 206 patients have been treated as part of the EAP at sites across the US (93 patients) and Europe (113 patients). No new signals or other safety concerns have arisen from the EAP.

8.5.2 Nonclinical Confirmatory Evidence

The overall nonclinical safety data are supportive of the clinical use of arimoclomol in the treatment of NPC. Key findings of the nonclinical safety and toxicology studies include the following:

- Arimoclomol was well-tolerated at exposure levels up to 5- to 10-fold (depending on species and study) above the human exposure.
- Carcinogenicity studies included a 2-year study in Han Wistar rats and a 26-week study in transgenic rasH2 mice; both studies demonstrated no carcinogenicity.
- Arimoclomol was neither mutagenic nor clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity [Ames], chromosomal aberration in Chinese Hamster Ovary cells, mouse lymphoma forward mutation, mouse and rat bone marrow micronucleus).
- A reduction in fertility and fecundity indices was noted for both sexes at 5-fold the recommended human exposure. Thus, it cannot be excluded that arimoclomol may adversely affect fertility.

8.6 Safety Conclusions

Overall, arimoclomol was well-tolerated and did not add to the high burden of disease. During the randomized, controlled double-blind phase of Study 002, there was a similar incidence rate of most AEs between arimoclomol and placebo treatment groups, and SAEs occurred less frequently among patients receiving arimoclomol as compared to placebo. Additionally, no unexpected safety signals were observed during the 4 years of open-label extension phase of Study 002 or the more than 3 years of Expanded Access NPC Program.

9. Benefit-Risk Conclusions

NPC is an ultra-rare, progressive, and fatal neurodegenerative disease, with a devastating impact on all aspects of life for patients, caregivers, and families.

At present, there are no therapies approved for NPC in the US. Treatment relies largely on symptom management and care from a multidisciplinary team. Thus, there is a high unmet medical need for effective and safe pharmacological treatments. The impact on patients with NPC and caregivers cannot be overstated, given the severe and debilitating nature of the disease and its high burden of care.

The MOA of arimoclomol is novel and targets the fundamentals of NPC etiology by both NPC1-dependent and NPC1-independent pathways: (1) via the NPC1-dependent pathway, the pool of functional and properly trafficked NPC1 protein is increased, thereby counteracting the primary etiology of the disease, and (2) via the NPC1-independent pathway, expression of CLEAR genes that encode a multitude of lysosomal proteins is broadly upregulated to mitigate the deleterious effects of impaired cholesterol trafficking and autophagy to improve overall cell health by increasing lysosomal biogenesis and autophagic flux.

Arimoclomol capsules were developed to support administration in a population comprising pediatric patients and patients with swallowing difficulties. They can be swallowed whole, or the contents can be sprinkled onto liquid or soft food, or the contents can be dissolved in water and administered through a feeding tube.

The results from the pivotal study demonstrated a clinically meaningful and statistically significant treatment difference in change from 4D-NPCCSS baseline score between arimoclomol and placebo in the primary analysis. Patients randomized into the arimoclomol group experienced a slower rate of disease progression with stabilization of NPC symptoms during the double-blind phase compared to placebo patients. The progression rate of the arimoclomol treated patients was also slower compared to no treatment in Study 001. Disease stabilization is a clinically relevant outcome for patients and families affected by this fatal and progressive neurodegenerative disease.

Converging confirmatory evidence across several clinical and nonclinical studies consistently aligns, reinforces, and confirms the benefit of arimoclomol demonstrated in the pivotal Study 002. Patients who switched to arimoclomol treatment in the OLE phase of Study 002 after one year of placebo in the double-blind phase, demonstrated a persistent slowing of disease progression. Importantly, the slowed progression in these patients remained stable through up to 4 years of treatment. Moreover, patients randomized to arimoclomol in the double-blind phase maintained a consistent progression rate through both study phases for up to 5 years of arimoclomol treatment. When arimoclomol patients were matched with an NIH natural history cohort, arimoclomol treatment resulted in slower disease progression over 4 years. Arimoclomol's MOA translated to tangible benefits in NPC mice with increased brain concentrations of mature NPC1 protein, improved rearing behaviors, and most importantly, increased survival.

Overall, arimoclomol was well-tolerated and did not add to the high burden of disease. There was a generally similar incidence of most AEs between arimoclomol and placebo. SAEs occurred less frequently in the arimoclomol group than in the placebo group. No unexpected

safety signals were observed based on the analyses of AEs during the OLE phase of Study 002 or during the more than 3 years of Expanded Access NPC Program.

At present, there is no cure and no approved treatment option for NPC in the US. Arimoclomol offers patients with NPC an effective, well-tolerated, and easy to administer therapy to address the significant unmet medical need in this ultra-rare, progressive, and fatal disease. The totality of data provides substantial evidence of efficacy and a positive benefit-risk profile supporting approval for the treatment of NPC.

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11. Appendix

11.1 Death Narratives

11.1.1 Study 002 Double-blind Phase

A female patient age 8 years with a history of dysphagia, aspiration of liquids, and seizures experienced epileptic encephalopathy and malnutrition approximately 6 months after starting arimoclomol, followed by respiratory distress a month later, and cardiopulmonary arrest approximately 8 months after starting Study 002. All events were consistent with NPC disease progression and assessed as not related to arimoclomol.

11.1.2 Study 002 Open-label Extension Phase

A female patient age 13 years with a history of seizures, elevated aspartate aminotransferase (AST), and scoliosis contracted lower respiratory tract infection approximately 1 month after starting treatment in the OLE. The infection progressed and could not be eliminated and became fatal approximately 2 months after starting the OLE. Treatment with arimoclomol was maintained throughout the illness, which was evaluated as severe and not related to trial drug.

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A male patient age 19 years experienced severe pneumonia, approximately 1 year after starting arimoclomol in the double-blind phase. The event resolved and was assessed as related to NPC disease and not related to arimoclomol. Approximately 10 months later, the patient had a serious and fatal event of aspiration pneumonia. The event was assessed as not related to arimoclomol.

11.2 Supplemental Safety Data

Table 40: Common Adverse Events Affecting ≥ 10% of Participants across All Indications (Population: Safety Set)

	Study 002 in NPC			Other Indications		
	Double-blind Phase		Open-label Extension	Double-blind Phase		Open-label Extension
Preferred Term, n (%):	Arimoclomol (N=34)	Placebo (N=16)	Arimoclomol (N=41)	Arimoclomol (N=362)	Placebo (N=219)	Arimoclomol (N=344)
Any AE	30 (88.2)	12 (75.0)	37 (90.2)	337 (93.1)	192 (87.7)	270 (78.5)
Constipation	7 (20.6)	3 (18.8)	5 (12.2)	61 (16.9)	31 (14.2)	26 (7.6)
Fall	2 (5.9)	0	2 (4.9)	60 (16.6)	36 (16.4)	27 (7.8)
Headache	3 (8.8)	1 (6.3)	4 (9.8)	56 (15.5)	35 (16.0)	15 (4.4)
Diarrhea	7 (20.6)	3 (18.8)	8 (19.5)	37 (10.2)	24 (11.0)	22 (6.4)
Nasopharyngitis	2 (5.9)	4 (25.0)	8 (19.5)	33 (9.1)	34 (15.5)	12 (3.5)
Nausea	0	1 (6.3)	1 (2.4)	46 (12.7)	13 (5.9)	17 (4.9)
Arthralgia	1 (2.9)	1 (6.3)	2 (4.9)	27 (7.5)	22 (10.0)	12 (3.5)
Upper respiratory tract infection	6 (17.6)	1 (6.3)	9 (22.0)	23 (6.4)	17 (7.8)	6 (1.7)
Vomiting	8 (23.5)	4 (25.0)	5 (12.2)	21 (5.8)	5 (2.3)	8 (2.3)
Cough	1 (2.9)	1 (6.3)	7 (17.1)	20 (5.5)	12 (5.5)	8 (2.3)
Pneumonia	0	2 (12.5)	3 (7.3)	17 (4.7)	13 (5.9)	13 (3.8)
Pyrexia	6 (17.6)	3 (18.8)	4 (9.8)	14 (3.9)	6 (2.7)	14 (4.1)
Bronchitis	4 (11.8)	2 (12.5)	7 (17.1)	10 (2.8)	13 (5.9)	3 (0.9)
Weight decreased	5 (14.7)	0	6 (14.6)	7 (1.9)	8 (3.7)	3 (0.9)
Epistaxis	2 (5.9)	1 (6.3)	5 (12.2)	8 (2.2)	3 (1.4)	6 (1.7)
Corona virus infection	0	0	7 (17.1)	1 (0.3)	1 (0.5)	11 (3.2)
Gastroenteritis	2 (5.9)	2 (12.5)	4 (9.8)	4 (1.1)	4 (1.8)	3 (0.9)
Rhinitis	5 (14.7)	2 (12.5)	5 (12.2)	3 (0.8)	1 (0.5)	0
Seizure	3 (8.8)	1 (6.3)	7 (17.1)	0	1 (0.5)	1 (0.3)
Epilepsy	1 (2.9)	2 (12.5)	5 (12.2)	0	0	1 (0.3)
Ear infection	0	2 (12.5)	1 (2.4)	2 (0.6)	2 (0.9)	1 (0.3)
Eye infection	0	2 (12.5)	2 (4.9)	0	1 (0.5)	0

AE = adverse event; NPC = Niemann-Pick, type C.
Note: Safety Set includes all participants who were either randomized and received ≥ 1 dose of study drug or participated in an open-label extension.