16 December 2021
EMA/177363/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

MIPLYFFA

International non-proprietary name: arimoclomol

Procedure No. EMEA/H/C/005203

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Invented name of the medicinal product:	**Miplyffa**
INN (or common name) of the active substance(s):	Arimoclomol citrate
Applicant:	Orphazyme A/S
Applied Indication(s):	Treatment of Niemann-Pick Disease, Type C
Pharmaco-therapeutic group (ATC Code):	Other nervous system drugs (N07)
Pharmaceutical form(s) and strength(s):	Hard capsules, 31 mg, 47 mg, 62 mg, 93 mg, 124 mg

List of abbreviations

AP	Applicant's Part (or Open Part) of an ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas chromatography
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
LDPE	Low Density Polyethylene
KGY	Kilogray
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PPM	Parts per million
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SPC	Summary of Product Characteristics
UV	Ultraviolet
XRD	X-Ray Diffraction

* This is a general list of abbreviations. Not all abbreviations will be used.

1. CHMP Recommendation

Based on the review of the data on quality, safety, efficacy, the application for Miplyffa, an orphan medicinal product, in the treatment of "Miplyffa is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older, in combination with miglustat and as monotherapy in patients not suitable for therapy with miglustat" is not approvable since a "major objection" has been identified, which precludes a recommendation for marketing authorisation at the present time. The details of this major objection are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies:

Clinical:

Currently there are two major objections:

- Efficacy has not been sufficiently demonstrated
- Uncertainty of maintenance of effect of arimoclomol in the OLE study

1.1. Questions to be posed to additional experts

The CHMP would like to obtain input from an *ad hoc* expert group (AHEG) with respect to the marketing authorisation application of arimoclomol product Miplyffa for treatment of Niemann-Pick disease type C in patients aged 2 years and older. Questions are stated below.

Questions to AHEG

1. Is the disease course in the control group as expected? Specifically, is it common to observe periods of stabilisation over several months alternating with sudden deterioration? To what extent are miglustat or other factors, e.g. disease stage or age, influencing the natural course of the disease?

2. Based on the available data, can efficacy and maintenance of effect be considered established, also taking into account the natural course of the disease and the heterogeneity of the target population?

3. The efficacy results are driven by the subgroup co-treated with miglustat. Do the (non-)clinical data support a conclusion on an additive or synergistic effect of arimoclomol to miglustat? If this is the case, can the effect in this subgroup be considered clinically relevant and convincingly established?

4. Is the safety profile sufficiently characterised and deemed manageable considering the target population?

1.2. Inspection issues

1.2.1. GMP inspection(s)

Not necessary.

1.2.2. GCP inspection(s)

No further inspection action is required.

1.2.3. New active substance status

Based on the review of the data the active substance arimoclomol citrate contained in the medicinal product Miplyffa is considered to be qualified as a new active substance in itself.

1.3. Additional data exclusivity /Marketing protection

N/A

1.4. Similarity with authorised orphan medicinal products

At present there is no authorised orphan medicinal product for a condition related to the proposed indication. There is no need to conduct orphan similarity assessment vis-à-vis Zavesca® (miglustat) as it is no longer covered by market exclusivity.

1.5. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The applicant applied for the following indication: "Miplyffa is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older, in combination with miglustat and as monotherapy in patients not suitable for therapy with miglustat".

2.1.2. Epidemiology

NPC is a rare, progressive, and fatal neurodegenerative disorder with an estimated incidence of ~1:100,000 live births (Geberhiwot et al. 2018). It is characterised by gradual loss of function that typically leads to death before adulthood. Overall, the mean life expectancy for patients with NPC is 13 years (Bianconi et al. 2019). It has substantial impact on all aspects of the life of the patients and their families.

NPC is an autosomal recessive disorder caused by mutations in the NPC1 (95% of cases) or NPC2 genes. Both genes encode lysosomal proteins that are essential in intracellular transport and metabolism of lipids. As a result of the dysfunction of either of these NPC proteins, lysosomal function is impaired causing an accumulation of lipids in the lysosomes, which in turn leads to cell stress and toxicity (Lloyd-Evans and Platt 2010; Platt et al. 2018). Over time, this leads to neurodegeneration as well as peripheral organ dysfunction.

2.1.3. Biologic features, aetiology and pathogenesis

NPC is a rare, progressive and debilitating neurodegenerative disease arising from mutations in the NPC1 or NPC2 genes, encoding lysosomal proteins that are essential in intracellular transport and metabolism of lipids. As a result of the mutations, NPC proteins are often misfolded and degraded prematurely, leading to impaired lysosomal function and accumulation of multiple lipid species (Lloyd-Evans and Platt 2010). Over time, this leads to neurodegeneration. Liver, spleen, and lungs may be

affected as well. The age of onset for NPC disease can vary greatly, from a neonatal rapidly progressive fatal disorder to an adult-onset slowly progressing neurodegenerative disease.

2.1.4. Clinical presentation, diagnosis and prognosis

The disease is characterised by a range of progressive and disabling symptoms including increasing difficulties with basic functions such as walking, motor coordination, swallowing, speaking, concentrating and remembering, leading to complete dependency on family and caregivers (Wraith and Imrie 2007). The progressive deterioration of brain function leads to a significant decrease in the quality of life of patients and their families (Benussi et al. 2018).

While manifesting most commonly during childhood and adolescence, NPC can present at any stage of life with highly diverse symptomatology and with variable speed and patterns of progression – from a neonatal, rapidly progressive fatal disorder to an adult-onset, slowly progressing, neurodegenerative disease. NPC can be categorised 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 is also predictive of rapid disease progression. Double functional null NPC1 genotype predicts an early infantile and severe NPC. No single symptom can predict the progression rate of the individual patient (Vanier 2010; Yanjanin et al. 2010).

Systemic signs of liver, spleen and lung involvement typically precede the disease-defining neurodegeneration. 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 ataplexy. The progression of the neurological symptoms is responsible for disability and premature death in most cases (Vanier 2010).

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. However, 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.

At the terminal stage, patients are bedridden with complete ophthalmoplegia and loss of volitional movements caused by severe encephalopathy with uncontrolled seizures. At this stage, therapy consist primarily of palliative care.

2.1.5. Management

At present there are no cure or disease-modifying therapies for NPC, and consequently there is a high unmet medical need for new treatment options (Geberhiwot et al. 2018).

Miglustat is authorised in the European Union (EU) for the treatment of progressive neurological manifestations in patients with NPC. Miglustat reversibly inhibits glucosylceramide synthase and thus works as a substrate reduction therapy.

The unmet medical need for novel treatment options remains high with patients continuing to have progressive neurodegeneration with fatal outcome. In a recent paper over an observation period of 50 years, 338 deaths caused by NPC with a mean age of 13 years were described and it was concluded that there was no significant change in survival over the last 20 years (Bianconi et al. 2019).

2.2. About the product

Arimoclomol capsules are available in five strengths expressed as arimoclomol base: 31 mg, 47 mg, 62 mg, 93 mg and 124 mg. It is easy to administer to patients with swallowing difficulties, including paediatric patients, as it is formulated in a capsule that can be opened and the content can be dispersed in liquid or soft food.

Pharmacological class
Arimoclomol citrate (N-[(2R,Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrate) is a synthetic chemical entity, also known as BRX-345. Arimoclomol is a heat shock protein amplifier.

Claimed indication
Initially proposed indication:

Miplyffa is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older.

Currently proposed indication:

Miplyffa is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older, in combination with miglustat and as monotherapy in patients not suitable for therapy with miglustat.

Mode of action
Arimoclomol is an orally available small molecule that crosses the blood brain barrier (BBB) (Cudkowicz et al. 2008). Arimoclomol amplifies and sustains the cellular production of heat shock proteins (HSPs), in particular, HSP70, through prolonged activation of heat shock factor-1 (HSF-1), and induction of the HSR (Kalmar et al. 2008; Neef, Jaeger, and Thiele 2011). HSP70 and other HSPs are critical to correct folding and processing of the integral lysosomal membrane protein NPC1, including misfolding mutations, which is the most common form of mutated NPC1 in patients suffering from NPC (Nakasone et al. 2014; Millat et al. 2001). The HSR is linked directly to lysosomal integrity through HSP70 mediated stabilisation of lysosomal membranes and protection from cell death (Kirkegaard et al. 2010; Petersen et al. 2010; Nylandsted et al. 2004). Thus, by amplifying the HSR, arimoclomol targets both protein misfolding and lysosomal dysfunction through a natural cellular defence mechanism. Arimoclomol therefore has a novel mechanism of action targeting the fundamentals of NPC aetiology: NPC protein misfolding and lysosomal dysfunction (Ingemann and Kirkegaard 2014; Neef, Jaeger, and Thiele 2011; Kirkegaard et al. 2016).

2.3. The development programme/compliance with guidance/scientific advice

Orphazyme is currently developing arimoclomol for 4 severe orphan diseases: NPC, Amyotrophic Lateral Sclerosis (ALS), Inclusion Body Myositis (IBM), and Gaucher Disease (GD).

The development programme for NPC consists of: 1 double-blind (DB), placebo-controlled trial in patients with NPC (CT-ORZY-NPC-002) including an ongoing open-label (OL) extension part (12 month data included in this submission), 1 observational trial in patients with NPC (CT-ORZY-NPC-001), 9 completed clinical pharmacology trials (including a recently completed trial in patients with hepatic impairment), PK assessments from 1 trial in patients with ALS, as well as 2 ongoing trials: a renal impairment trial. A QT/QTc (TQT) interval prolongation trial was recently finished and included in the D120 dossier.

The development programme is supported by safety data from completed and ongoing trials in other indications.

The pivotal phase 2/3 trial CT-ORZY-NPC-002 was mainly conducted in the EU region (12 sites out of 14 sites), with only few patients recruited at the 2 remaining US sites.

All trials were conducted according to the ethical principles originating from the Declaration of Helsinki and in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice. In addition, all relevant local regulatory requirements were followed.

Orphan drug designation (ODD) for arimoclomol citrate for the treatment of NPC was granted from the European Commission on 19 November 2014.

A total of 5 Protocol Assistance Procedures have taken place with European Medicines Agency (EMA) to discuss quality, nonclinical and clinical aspects of the development programme for arimoclomol citrate for NPC. Non-clinical advice was provided in procedures EMEA/H/SA/3709/1/2017/PA/SME/III, EMEA/H/SA/3709/3/2018/PA/SME/II, EMEA/H/SA/3709/3/FU/1/2019/PA/SME/II, EMEA/H/SA/3709/1/FU/1/2019/PA/SME/III and EMEA/H/SA/3709/1/FU/1/2019/PA/SME/III (clarification letter). In these protocol assistance procedures, the applicant sought advice on potentially genotoxic impurities, toxicity testing of the three main metabolites of arimoclomol, completeness of the non-clinical study programme for MAA, the possibility to submit carcinogenicity studies as post-authorisation measure, and the need to conduct mechanistic studies on the observed cataracts in a particular rat repeated dose toxicity study. The advices provided by CHMP and a discussion on whether the advice s were sufficiently followed in this MAA can be found in the non-clinical assessment report under section 1.1. Clinical aspects of the development programme including the trial design in relation to a future Marketing Authorisation Application (MAA) was discussed in February 2018 (Final Advice March 2018), and data from the CT-ORZYNPC- 002 trial in support of an MAA was presented in the Protocol Assistance with final advice in June 2019. The obtained advice s are summarised in Table 1-1. The 3 other Protocol Assistance concerned the quality development programme. Furthermore, pre-submission meetings have been held with the EMA product team, the CHMP Rapporteur, PRAC Rapporteur, PRAC Co-Rapporteur, as well as the CHMP Co-Rapporteur.

Table 1-1 Summary of Key Regulatory Authority Agreements Relevant for the Clinical Development in NPC

Question	Advice received
CHMP, Feb 2018, [M1.2 Application Form, EMEA/H/SA/3709/1/2017/PA/SME/III]	
5-domain NPCCSS as the primary endpoint for the evaluation of treatment differences (treatment arms vs. placebo)	Advice to focus on a few highly clinically relevant neurological domains for the primary efficacy analysis and determine minimal important clinical difference.
Clinical safety database to support MAA	Size of the safety database is deemed acceptable provided that no major safety signal emerges during clinical development. Follow-up safety data collection will be a requirement to be agreed in a RMP
Significant benefit of arimoclomol to current treatments	Sufficient number of patients on miglustat therapy should be included as COMP will focus their determination of significant benefit on these patients
CHMP, May 2019, [M1.2 Application Form, EMEA/H/SA/3709/1/FU/1/2019/PA/SME/III]	
Deferral of trial investigating the effect of renal function on the PK of arimoclomol until after MA	Acceptance of proposal to defer the study on PK properties of arimoclomol in patients with renal impairment post-approval.
Individual presentation of safety data from trials conducted with arimoclomol	Acceptance of proposal to analyse and present safety data separately provided no major safety signal emerges during clinical development. In addition, pooled safety data within an indication/population are expected. Safety data from other indications are considered supportive.
Data from patients on miglustat therapy for evaluation of significant benefit	General trial design allows for assessment of significant benefit

2.4. General comments on compliance with GMP, GLP, GCP

GMP:

Regarding the GMP documentation presented in Module 1, please refer to the separate overview document.

A QP declaration is provided concerning GMP compliance of the two manufacturers.

In Annex 5.9 of Module 1, an establishment inspection report for the manufacturer of the intermediates PCO-N-oxide and azonia is provided.

GLP:

All pivotal safety pharmacology and toxicology studies were conducted in GLP compliance. No concerns were identified.

GCP:

The applicant provided a statement that all clinical studies were conducted in compliance with ICH GCP E6 2016 and with the ethical principles that have their origin in the Declaration of Helsinki.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

2.5.2. Accelerated assessment

The applicant has not requested accelerated assessment.

2.5.3. New active substance status

The applicant requested the active substance arimoclomol contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

2.5.4. Orphan designation

Miplyffa, was designated as an orphan medicinal product (EU/3/14/1376) on 19 November 2014 in the following indication: treatment of Niemann-Pick disease, type C.

2.5.5. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.6. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0213/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0213/2018 was not yet completed as some measures were deferred.

The deferred measure is a paediatric sub-study to the open label extension phase of the pivotal clinical trial CT-ORZY-NPC-002 with the objective to study the safety and tolerability of arimoclomol in paediatric patients aged 6 months to 2 years.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as capsules, hard containing 31, 47, 62, 93 or 124 mg respectively of arimoclomol citrate as active substance.

Other ingredients are microcrystalline cellulose and magnesium stearate (capsule content).

For the capsule shells:

Miplyffa 31 mg: hypromellose, titanium dioxide, brilliant blue FCF-FD&C Blue 1;

Miplyffa 47 mg: hypromellose, titanium dioxide, brilliant blue FCF-FD&C Blue 1, yellow iron oxide;

Miplyffa 62 mg: hypromellose, titanium dioxide, yellow iron oxide;

Miplyffa 93 mg: hypromellose, titanium dioxide, yellow iron oxide, red iron oxide;

Miplyffa 124 mg: hypromellose, titanium dioxide, red iron oxide.

Printing ink: shellac, black iron oxide, propylene glycol, ammonia, potassium hydroxide.

The product is available in high density polyethylene (HDPE) bottles with a child-resistant closure.

3.1.2. Active Substance

3.1.2.1. General information

Arimoclomol is a new active substance that is not subject of an official compendium. Full information of the active substance is given in the dossier. Information regarding nomenclature, structure and general properties is provided. Arimoclomol is a chiral molecule containing one chiral centre (R-enantiomeric form) and is provided as a white to off-white crystalline powder. Solubility, pH, thermal properties, hygroscopicity, chirality, isomerism and polymorphism have been investigated. It is highlighted that it is slightly hygroscopic, presented as the R-enantiomeric form and consistently observed in polymorph form 1.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The manufacturing process for arimoclomol citrate active substance is depicted in a flow chart and described in a narrative description. It is a six-step manufacturing process (last step: crystallisation).

Provided flow charts include molecular formulae, weights, chemical structures of starting materials, intermediates, reagents and identifies solvents. Critical process parameters and in-process tests are highlighted in the narrative description which is regarded as acceptable. All relevant process parameters are submitted. Quantities or ranges of materials used in a current representative production scale batch are outlined next to yields and yield ranges. Several critical steps have been identified. No class 1 solvents and no catalysts are used. Information on batch size is provided: the batch range of arimoclomol citrate final active substance is 25-250 kg. Sodium nitrite is used in step 3 of the manufacturing process. Appropriate risk assessment regarding possible nitrosamine impurities has been provided.

Materials used in the manufacture of the active substance (starting materials, reagents, solvents and auxiliary materials) are listed including information where each material is used. Information provided by the applicant is acceptable.

Proposed starting materials: Piperidine, epichlorohydrin and 3-cyanopyridine are the proposed starting materials for the commercial manufacturing process of arimoclomol citrate. Respective suppliers, synthesis schemes, specifications and purity test methods are provided.

Reagents, solvents and auxiliary materials: Specifications of solvents, reagents and auxiliary materials used in the manufacture of arimoclomol citrate active substance are provided. No recovered solvents are used in the synthesis of arimoclomol citrate. Catalysts are used in the starting material synthesis. None of the specifications for the originator solvents used include a routinely performed test and limit for the class 1 solvent benzene. However, benzene is specified in the active substance specification with a limit. Therefore, control of benzene is regarded as suitable. Confirmation that the manufacturing

process to synthesise arimoclomol citrate does not utilise any materials of animal or human origin is given.

Control of critical steps: Information on controls of critical process parameter is given. Acceptance criteria are provided, and the analytical procedure are briefly described.

Intermediates: A total of five intermediates are isolated: PCO-N-oxide, azonia, ORZY-01 (BRX-197), ORZY-03 (BRX-344), and ORZY-04 (Crude BRX-345). Specifications are provided and key validation data like validated range, LoQ and LoD are provided for the control methods. ORZY-03 is controlled with the same test method as used for the release testing of the final substance. Complete specifications are provided.

Manufacturing process development

The process development programme summarises the differences from the current manufacturing process and the manufacturing process used during clinical development. Process transfer from one manufacturing site to a new manufacturing site has been completed. Manufacture of active substance intended for commercial use took place in 2021. The applicant has described in detail all manufacturing steps, all process parameters and controls thereof. Moreover, quality attributes and process parameters that have been shown to impact the quality of the active substance are discussed. It is stated that in clinical trials batches manufactured from all three manufacturers have been used.

Characterisation

Structure of arimoclomol citrate is confirmed using suitable methods. Respective data/chromatograms/ spectra are given.

Impurities:

All potential impurities are described.

The S-enantiomer and other impurities are controlled in the active substance specification with a toxicologically qualified limit.

Inorganic impurities are controlled by the test residue on ignition/sulphated ash harmonised method with a limit of NMT 0.1% in the active substance which is acceptable.

No elemental impurities are intentionally added to the process. Therefore, a risk assessment regarding elemental impurities would be expected on the finished product level. However, the applicant has tested the active substance for various elemental impurities using a validated ICP-MS method where no elemental impurities were identified above the LoQ in any of the originalvalidation batches.

Some potential impurities are regarded as potentially genotoxic and controlled in accordance with guidelines.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The applicant has provided an active substance specification containing the parameters description, identification of arimoclomol citrate (FTIR), identification (chiral HPLC), purity (area %), assay (% w/w, anhydrous basis), related substances (% w/w), enantiomeric purity (area %), residual solvents, residue on ignition/sulphated ash and water content (Karl Fischer).

Analytical procedures and reference standards

The analytical procedures used to test arimoclomol citrate are all adequately described. Spectra/chromatograms are provided where applicable. Instrument operating conditions and calculations are listed where necessary.

The applicant provided full validation and validations summaries of the analytical procedures for testing assay/related substances/chromatographic purity, identity/enantiomeric purity, and residual solvents/benzene.

In order to allow establishment of the retest period for active substance manufactured by the new manufacturing site based on stability data from batches manufactured by the original manufacturing site, similarity of release data of batches used for stability testing has been confirmed. Batch data show compliance with respective limits, no OOS is found. Thus, consistent quality is ensured.

The currently used reference standard is Batch 16-2649-BRX345. Appearance, identification (^{1}H, ^{13}C-NMR, mass spectrometry, elemental analysis), purity, chiral purity, water content, residue on ignition, residual solvents and assigned potency have been investigated.

Up-to-date CoA of potential impurities reference standards are provided.

Batch analysis

Batch data are provided. All results comply with respective specification limits. As supporting data, batches used during clinical phases 2/3 are provided also showing compliance with proposed acceptance criteria.

No control of microbiological quality of the active substance is proposed. Justification is provided. This is considered acceptable bearing in mind the intended use of the active substance in the product.

Full information regarding the process at the original manufacturer is provided, however it is stated that the new manufacturer will use the same manufacturing route and plans to manufacture its first three batches. In response to d120, batch data from batches manufactured at the new manufacturer have been submitted showing compliance with set specification limits. Batches are confirmed to be set on stability.

Container closure

The primary packaging of arimoclomol citrate active substance is a bag of low-density polyethylene (LDPE) placed in a second LDPE bag which is further placed in a closed container (HDPE drum or equivalent). A specification of the primary container closure component is provided. The conformity of the primary packaging to the EU regulation 10/2011 incl. amendments has been submitted.

3.1.2.4. Stability

Six batches of arimoclomol citrate active substance, manufactured at the original manufacturer are set on stability testing (all manufactured between 02/2018 and 05/2019) next to the three batches manufactured at the new manufacturer. Long term results (25°C/60% RH) and accelerated data (40°C/75% RH) are available for up to 24 and 6 months, respectively, and 1M data for the new manufacturer. No OOS occurred and no trend can be observed. Supporting stability studies are provided (manufactured between 04/2008 and 08/2017). These data show similar results during shelf-life, however, as the manufacturing process has slightly changed these data are not taken for assessment.

A photostability study was carried out according to ICH Q1B. It is concluded that arimoclomol citrate should be stored protected from light which is acceptable. Further, stress studies showed that the

active substance slightly degrades under alkaline and photolytic stress (very slight degradation under oxidative stress). Used analytical methods are regarded as stability-indicating.

The active substance is therefore regarded as stable and a retest period for 24M when protected from light would be acceptable for active substance manufactured by either manufacturing site as the active substance is similar at release and thus, consistent quality is ensured.

Accelerated storage showed no increase in degradation impurities nor decrease in assay. The proposed storage condition (protected from light) is acceptable.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

Description and composition of the finished product

The finished product is presented as Capsules containing 31mg, 47 mg, 62 mg, 93 mg, and 124 mg of arimoclomol. Details of the empty hydroxypropyl methyl cellulose (HPMC) capsules used to fill the formulation blends are provided. The capsule shell body is imprinted in black with '31', '47', '62', '93' and '124', and 'OZ' on all caps. An adequate description of the five strengths of the finished product is presented. The composition is given, the function and the amount of each excipient is presented as mass per capsule.

There are no overages added to the formulation.

Pharmaceutical development

The active substance arimoclomol citrate is a highly soluble substance, classified as BCS class 1. It is physically and chemically stable and no interaction to the excipients could be detected.

The excipients are microcrystalline cellulose and magnesium stearate, both are from compendial quality. The capsules are made from HPMC, coloured depending on strength. Compliance of the colorants to Commission regulation 231/2012 is given.

The ink constituents Shellac, propylene glycol, strong ammonia solution and potassium hydroxide are in compliance to Ph. Eur, the pigment iron oxide black is registered as E172.

The finished product is intended to be used for children and adequate information thereof is provided.

The proposed finished product has been developed by a Quality by Design (QbD) concept. The Quality Target Product Profile (QTPP) was introduced during initial formulation development and updated throughout further development steps. Identification of Critical Quality Attributes (CQAs) was based on the severity of harm to patients (safety and efficacy) resulting from failure to meet that quality attribute of the finished product, the relative risk ranking system was used. Design spaces have been proposed for several steps in the manufacture of the finished product, which are sufficiently justified and described.

The early development started with strengths from 16 mg to 248 mg manufactured by manual wet granulation of arimoclomol citrate mixed with microcrystalline cellulose and talc, originally filled into gelatine capsule shells. Later on it was changed to HPMC capsules and talc was substituted with magnesium stearate.

To show comparability of the capsules at different development stages a bio waver was provided. The capsules from early development stage are not fully comparable in dissolution behaviour, as gelatine capsules have a faster release than the HPMC capsules. Nevertheless, all active substance is dissolved

at least after 15 minutes for all compositions. Therefore, the differences are not relevant for the bioavailability in the small intestine.

Development of dissolution method was described . The applicant states that the *in vitro* dissolution test was originally developed for the first Phase 2 finished product, i.e. a hard gelatine capsule containing a wet granulated blend of active substance, MCC and magnesium stearate. Selected method was used throughout formulation development with some adaptions to accommodate changes to the finished product formulation. The applicant has provided acceptable justification for development of the dissolution method without demonstration of the discriminatory power of the method (in accordance with Decision Tree #7.2 in ICH Q6A).

The acceptability/palatability of the finished product was evaluated in clinical phase 2/3 and was found to be acceptable at the majority of patients. Considering that this medicinal product is intended for the paediatric population, requirements of guideline of pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) have been taken into account.

In the manufacturing process development, a DoE was performed. The applicant has justified validity of developed Design Space also at commercial scale.

A maximal holding time of up to 29 days storage as blend in bulk (tote bin in the production area), and an additional maximal holding time of bulk capsules of 24 months has been confirmed (data for storage of 24 month was presented).

The finished product is stable over time across dosage strengths in the to-be-marketed container closure system, HDPE bottles.

The content of the capsule can be easily suspended in 20 mL water to be administered through a feeding tube or can be sprinkled on soft food and beverages with different texture, viscosity and pH, without any loss of potency for at least 24 hours.

3.1.3.2. Manufacture of the product and process controls

Manufacture

The batch formula is based on 47.5 kg lots for low strength blend and for high strength blend, no overages are used. The low strength blend is used for strengths 31 mg, 47 mg and 63 mg, the high strength blend for 93mg and 124 mg.

The manufacturing process is sufficiently described and all relevant process parameters are stated in the detailed process description (not part of this report) and in the description of control of critical steps. Holding of final blend (in mixing drum) and bulk product (in PE bags) is indicated in the description of the manufacturing process. Both are discussed in the development of the manufacturing process. Furthermore, the applicant has evaluated stability of bulk product over a period of 24 months, proposed holding times have been indicated. The quality requirements for the bulk packaging are laid down in the section P.7. Compliance with requirements of NfG on Start of Shelf Life of the Finished Dosage Form (CPMP/QWP/072/96) is confirmed considering the day of the first mixing of active substance with excipients as the start of shelf life for the finished product.

IPC testing is performed after encapsulation and after filling, frequency of testing and sample size is given. Critical process parameters are defined, information is consistent with conclusions of DoE. Design Space is claimed for manufacturing process based on two DoE studies, PAR for blending, roller compaction, lubrication and encapsulation were investigated.

Although a design space is claimed, the manufacturer states that the manufacturing process for commercial batches is conducted at the target values.

Arimoclomol capsules are considered a standard product manufactured by a standard process. A sufficient process validation has been performed on seven process validation batches, four with the low blend strength and three with the high blend strength.

Control of excipients

For the compendial excipients microcrystalline cellulose and magnesium stearate (non-animal origin), used in the granules, sufficient CoAs are provided.

The components of the capsules are not listed as single excipients with own specifications, but as "ready to use" capsules. Despite of the colorants all used components are in compliance to Ph. Eur. Functionality related characteristics described in the Ph. Eur. monograph of the respective excipients are controlled in specifications of microcrystalline cellulose and magnesium stearate.

The provided specifications and CoAs are exemplary and do not cover all colorants.

The finished product manufacturer's specification and CoA for the hydroxypropyl methylcellulose (HPMC) capsule shell is provided in the dossier.

Product specification, analytical procedures, batch analysis

Control of finished product

The specification covers all five strengths of the finished product, solely the description is given in one part for each strength. All capsules are from the same size, but colour and printing are different. The identification is made by two different techniques, HPLC and UV. Assay is in the range from 95 – 105% and related impurities are specified as "individual unspecified" with NMT 0.1% and "total" with NMT 0.5%. The uniformity of dosage units is controlled with even tighter limit than set in Ph. Eur., the dissolution is specified with NLT 85% (Q) within 30 minutes. The water content is limited with NMT 6%. Microbial quality is sufficiently controlled for an oral dosage form.

The analytical procedures are all listed in the dossier and adequate descriptions are provided.

Validation summaries of in-house methods have been provided. Full validation reports of in-house methods (assay, identification and content uniformity, related substances, dissolution, water content and microbial quality) have been provided . Stability indicating properties are demonstrated by forced degradation studies of assay and related substances. Batch data are presented for six batches, three for the low strength blend and three for the high strength blend, all manufactured at end of 2018 and packed in 185 mL HDPE bottles and one bulk of the 31 mg strength packed into PE bags.

For impurities related to the active substance it is referred to the active substance part of the dossier, for nitrosamine risk assessment and residual solvents sufficient reports are provided in the dossier. An elemental impurities risk assessment has been performed.

The justification for specification covers sufficiently all parameters.

Reference standards or materials

Reference standards are the same as for the active substance.

Container closure system

The primary packaging consists of HDPE bottles and a HDPE screw caps, both compliant to Commission Regulation (EU) No 10/2011. The inner sealing "safeguard plus" is also in compliance to EU regulation 10/2011 including EU regulation 321/2011.

A brief description of the secondary packaging is provided.

Specification as well as compliance with the requirements of Commission Regulation (EU) No 10/2011, Ph. Eur. 3.1.4 statement is provided for bulk packaging PE bags. It is mentioned that packaging is child resistant and corresponding certificate of compliance is submitted.

Stability of the product

Stability studies are performed on all strengths (started at November 2018) in the original packaging and at the bulk material stored in PE liner drums. Also, some supportive studies from technical and clinical batches are presented. In addition to this, in use stability studies, photostability studies, forced degradation studies (effect of heat, base and photodegradation) and freeze/thaw studies have been performed.

All studies show that the finished product is stable over time at all conditions.

The proposed shelf life of 30 months without temperature restrictions is acceptable, the finished product should be stored in original container to be protected from light. Future long term storage tests will be performed at 30°C, which is acceptable.

The in-use stability studies of 30 days and additional 3 months open dish studies are provided by the applicant. All results comply with specification, therefore no in-use shelf-life restriction is necessary.

3.1.3.3. Post approval change management protocol(s)

N/A

3.1.3.4. Adventitious agents

N/A

3.1.3.5. GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The provided documentation regarding active substance and finished product is acceptable as all initially raised issues have been solved adequately.

3.2. Non clinical aspects

3.2.1. Introduction

Arimoclomol (Miplyffa) is indicated in the treatment of Niemann Pick disease type C by supposedly activating the intracellular heat shock response. This way, arimoclomol is claimed to achieve stabilisation of the lysosomal integrity and restoration of misfolded NPC1 mutations in Niemann-Pick Type C disease.

An extensive non-clinical pharmacology, pharmacokinetics and toxicology dossier together with an environmental risk assessment were submitted.

3.2.2. Pharmacology

Niemann-Pick disease type C (NPC) belongs to the larger group of diseases known as lysosomal storage disorders (Platt et al., 2018). NPC is a rare progressive autosomal recessive genetic disorder characterised by an inability of the body to transport cholesterol and other (sphingo)lipids inside of cells. NPC is caused by mutations in the NPC1 gene (NPC type 1C in 95%) or the NPC2 gene (NPC type 2C, in 5%), which are both lipid transporters located in the lysosomes. As a consequence of this genetic disorder, abnormal accumulation of lipids are observed in the lysosomes and retention of mutated NPC1 protein in the endoplasmic reticulum. These accumulations lead to enhanced degenerative processes like autophagy and cell death. Patients suffer from these degenerative processes predominantly in the central nervous system, liver, spleen and lung.

Arimoclomol is an orally available small molecule intended to be administrated to NPC patients aged 2 years and older. Depending on age and weight of the patients the proposed arimoclomol dose varies from 31 mg to 124 mg and should be given three times a day with or without food.

The rational for arimoclomol administration is based on observations that expression of the transcription factor HSF1is enhanced, leading to the induction of the heat shock response (HSR), HSP70 and mature NPC1 protein. Thereby, the application of arimoclomol should lead to stabilisation of the lysosomal integrity and restoration of misfolded NPC1 mutations in Niemann-Pick Type C disease.

Primary pharmacology was shown *in vitro* in NPC patient derived fibroblasts and heterologous cellular systems as well as in a murine $NPC^{-/-}$ animal model. Fibroblasts from skin biopsies of NPC1 patients and NPC1-/- mice represent appropriate preclinical *in vitro* and *in vivo* systems to establish primary pharmacology.

The exact target mechanism for arimoclomol is unknown. However, application of up to 400 µM arimoclomol significantly increased HSF1, HSP70 and the NPC1 cholesterol transporter in human fibroblasts from NPC1 patients (but not below 100 µM). Taken together, a concentration of 400 µM arimoclomol is considered to significantly enhance the heat shock response and processing of mature glycosylated NPC1 proteins.

Conversely, already 10 and 50 µM arimoclomol significantly restored lysosomal structure and lipid content in this compartment of fibroblasts with the most abundant I1061T mutation. Thus, it is hard to understand how arimoclomol (10 and 50 µM) contributes to significant reduction in lysosomal cholesterol without effects (<100 µM) on the expression of the transporter NPC1 or HSP70? Moreover, in secondary pharmacology arimoclomol was used to compete with radioligands at 10 µM in ligand binding assays. Thus, a stringent concentration-response relationship or EC_{50} values for arimoclomol are not provided by the applicant. Discussion regarding correctly processed NPC1, unesterified cholesterol levels and lysosomal area was provided for other NPC mutations in patient fibroblasts. It was confirmed that arimoclomol has a less pronounced effects in fibroblasts with mutations other than I1061T indicating that arimoclomol would similarly exert a variable efficacy among patients harbouring different mutations in NPC1 protein. As previously shown, a concentration dependant arimoclomol effect on the total NPC1 protein can be observed in all tested fibroblast cell lines suggesting that a treatment related improvement should be present among all genotypes.

The applicant expanded the knowledge on arimoclomol induced effects in four additional *in vitro* studies in response to the D180_LoQI and postulates that arimoclomol activates the transcription factor TFE3 and thereby the "coordinated lysosomal expression and regulation" (CLEAR) network of genes, including NPC1 and NPC2.

In human wild type (wt) fibroblasts eight out of ten selected CLEAR genes were significantly activated on mRNA level by 5-day arimoclomol (400 µM) treatment (Study DOC-2110140041), but not

transcription factors TFE3 and TFEB. The latter finding is somehow puzzling since also in human wt fibroblasts arimoclomol increased significantly TFE3 binding to the promotor of CLEAR target genes like NPC1, NPC2 in ChIP experiments of study DOC-2110090039, indicating that regulation of TFE3 is not on transcriptional level.

Nevertheless, in wt and patient-derived fibroblasts 400 µM arimoclomol enhanced nuclear translocation of TEF3 within one day of incubation (study DOC-2110130040). Moreover, in two patient derived fibroblast cell lines 400 µM arimoclomol significantly enhanced the mRNA of NPC1, HSPA1A and GBA at 2 and 5 days of incubation (study DOC-2110140042). Concentrations below 400 µM arimoclomol were not able to augment these target genes significantly. Further, it is difficult to understand why the other eight CLEAR network genes listed in Tab.3-1 of study DOC-2110140041PCR were omitted in this study and thus only analysed in wt fibroblasts.

The three most abundant arimoclomol metabolites in humans at steady state (M2, M5 and M105) were ineffective with respect to the induction of HSP70 and enhancement of NPC1 protein levels in human fibroblast cells from NPC1 patients.

Arimoclomol was also investigated *in vivo* in an $NPC^{-/-}$ mouse model. The animal model mimics the impairments of NPC disease and is therefore considered suitable to evaluate efficacy of arimoclomol. Importantly, 30 mg/kg arimoclomol significantly enhanced the overall survival of $NPC^{-/-}$ mice (Kirkegaard et al. 2016). Arimoclomol was orally applied in daily doses of 1-300 mg/kg (Kirkegaard et al. 2016; study no. CRO-1211210031). While data within the publication Kirkegaard et al. are consistent, this is not the case if including the data from study no. CRO-1211210031 (Kirkegaard et al. 2016).

The effect of arimoclomol in *Npc1* -/- mice provides evidence that arimoclomol targets NPC aetiology. Arimocolomol (10 mg/kg orally) significantly activates HSF1 and augments HSP70 protein levels in brains, but not in liver tissue of *Npc1* -/- mice, which may be due to different expression of HSF1 and nuclear turnover in this tissue.

Significant improvement on locomotion parameters such as cadence, diagonal support, support three, stand, step cycle, initial dual stance and terminal dual stance improved under arimocolomol treatment in *Npc1* -/- mice. However, a stringent dose-dependency of arimoclomol induced effects is not provided. There is no ED_{50} calculated or provided so that one cannot estimate a safe and effective dose in *Npc1* -/- mice. Most of the arimoclomol data provided by Kirkegaard et al. were generated with 10 mg/kg orally (Kirkegaard et al. 2016). But again, as depicted in Fig. 8A therein, the highest concentration of arimoclomol (30 mg/kg) was significant only in one out of three different gait analyses. The applicant explains in part these discrepancies by unknown strain differences, using *Npc1-/- mice* from CRO(QPS) or from University of Oxford result in in different onset and severity of the phenotypes. Nevertheless, arimoclomol was not significant inside rearing experiments up to 300 mg/kg in study no. CRO-1211210031 but significant in Kirkegaard et al. already at 10 mg/kg arimocolomol (Fig. 8B in Kirkegaard et al. 2016). Although the improvement of gait parameters is shown for some concentrations a consistent dose dependent amelioration of motor function is not provided. Thus, discrepancies in efficacy between the motoric analyses between Kirkegaard et al. 2016 and study no. CRO-1211210031 may stem from using *Npc1*-/- mice of different souces (CRO(QPS) versus University of Oxford). Hence, it is difficult to understand a causal dose-effect relationship of arimoclomol comparing *in vivo* with *in vitro* effects.

Arimoclomol was shown to improve gait parameters in the absence of NPC1 protein. It is suggested that arimoclomol activates HSF1 and increases levels of HSP70 which in turn improve lysosomal function within the CNS, reduce lipid storage, improve myelination and preservation of cerebellar structures. This provides an alternative mechanism of action of arimoclomol in the absence of NPC1 protein and supports the improved locomotion results in mice.

Also in response to the D180-LoQI the applicant submitted a draft study report (CRO-1707310132) in an Npc1-/- mouse model, investigating the survival and behaviour in presence of arimoclomol and miglustat combinations. Median survival days of controls increased under arimoclomol 30 mg/kg/d in drinking water from 84.5 days to 90 days and under miglustat (600mg/kg/d) exposure to 120 days. The combination of arimoclomol plus miglustat significantly extended the median lifespan to 143 days and thereby was more effective than arimoclomol alone. Although overall survival was significantly enhanced by the combination of arimoclomol and miglustat compared to miglustat alone, no such effect was seen in any time point (6, 8, 10 or 12 weeks) or functional test, like motor coordinations (RotaRod), motor functions, tremor (quantitative monitor), SmithKline Beecham, Harwell, Imperial College, Royal London Hospital, phenotype assessment (SHIRPA) and gait analyses. Moreover, the effects of arimoclomol alone were always inferior compared to miglustat alone. However, these data were not statistically analysed by the applicant, except for the overall survival, which was significantly reduced with arimoclomol (median 90 days) compared to miglustat (median 120 days).

A broad secondary pharmacology programme was conducted to identify possible off-target effects of arimoclomol *in vitro*. In competition binding assays specific radioligands were co-administrated with 10 µM arimoclomol. An agonistic interaction of arimoclomol with $GABA_A$- and $GABA_{A1}$ (α1β2γ2)-ion channels (study No. 100031800) was not confirmed in subsequent studies (study No. 100046132 and FR095 0007433). Conversely, an antagonistic effect of arimoclomol on ET_A- or 5-HT_{2B}-receptors was observed (study No. 100046132 and TW04-0003354). Insolubility of arimoclomol in the stock solution was observed in the functional assay (study No. TW04-0003354) which might have reduced the effective concentration and as a consequence the true IC50 value might be lower than the reported 28 µM. Despite of that, warnings added in the SmPC sections 4.3, 4.6 and PIL section 2 reflect antagonistic effect on ET_A and this issue is therefore considered minor. Safety pharmacology studies with arimoclomol were conducted in accordance with the ICH S7 guidelines to assess the effects of arimoclomol on vital organ functions, in particular on cardiovascular, respiratory and central nervous system (CNS) effects.

The intravenous application of arimoclomol induced a transient depression of blood pressure and heart rate in anaesthetised rats and was more pronounced in female rats. These results were recapitulated in another study to a lesser extent at lower concentrations of arimoclomol. Nevertheless, in anaesthetised dogs no alteration in haemodynamic parameters was observed up to 10 mg/kg arimoclomol (iv.).

The most abundant human arimoclomol metabolites, M2, M5 and M105 were evaluated for hERG inhibition in study No. PS19F739. Noteworthy, at 7 µM M2 and M105 mediated a hERG inhibition of 21.0% and 27.8, respectively. Arimoclomol at 7 µM inhibited hERG currents by 4.7%. For comparison, Cmax values for arimoclomol, M2 and M105 in the clinical setting are 3.4 µM, 1.14 µM and 0.84 µM, respectively, and are considered to be below concentrations which mediated hERG inhibition in the *in vitro* assays. Nevertheless, arimoclomol, M2 and M105 mediated effects on hERG activity were not or only partially reversed after the washout period. The QTc intervals were assessed in several repeat-dose toxicity studies in dogs and revealed a 10% QTc prolongation. Notably, adverse effects including reduced food consumption and body weight loss as seen in the 2-week repeat-dose dog study can influence the electrical activity of the heart. Nevertheless, considering arimoclomol as a long-term therapy hERG inhibition and slight QTc prolongation are deemed to exert arrhythmic potential and a concern was raised on this issue further below.

The modified mouse Irwin test was performed to evaluate the effect of arimoclomol on the CNS. The study revealed increased scores in e.g. arousal, positional and spontaneous activity, locomotion, wire manoeuvre, posture changes and touch-escape reaction at ≥100 mg/kg arimoclomol, which indicated a slight and transient excitation of the CNS. Enhanced arousal and positional/spontaneous activity were pronounced in female mice.

In supplemental safety pharmacology studies, arimoclomol increased the pentobarbital-induced sleeping duration ≥200 mg/kg, but did not affect hypnotic onset time. The number of clonic convulsions evoked by pentetrazol were slightly decreased at ≥100 mg/kg possibly indicating an anticonvulsant effect of arimoclomol, which was not observed in electrically stimulated convulsions. Additionally, an analgesic effect was observable in CFLP mice using the acetic acid-induced writhing model, no such an effect was seen in the tail flick response to radiant heat-induced pain in Wistar rats.

The muscle relaxant zoxazolamine induced paralysis was not enhanced or prolonged by the addition of 100-400 mg/kg arimoclomol pretreatment for three days.

Renal function was assessed in two rat studies. In the first study, a single oral administration of arimoclomol elevated urinary volume and induced a slight increase in excretion of sodium and chloride. Creatinine clearance was elevated at the highest dose of 400 mg/kg in male rats only. The second study explored the pharmacodynamic interaction between arimoclomol (20 mg/kg/day) and the loop diuretic furosemide after 2 weeks of daily oral dosing to hypertensive rats. Arimoclomol again increased urinary volume and the excretion of creatinine, potassium, phosphorus, protein and uric acid, whereas furosemide at the same dose increased the urinary volume, as well as the excretion of sodium, potassium, and calcium. When combined, arimoclomol and furosemide further increased several urinary endpoints suggesting an additive effect of this drug-drug interaction. Although elevated urinary volume and increased urinary electrolyte excretion was observed in rats following arimoclomol treatment, similar effects were not observed in dogs. In clinical trials diuretic effects of arimoclomol were not confirmed. Thus, this effect appears to be specific to rats and could be considered to be of limited clinical relevance.

Arimoclomol had no effect on respiratory rate, tidal volume, body temperature or intestinal smooth muscle contraction.

Pharmacodynamic drug interactions were investigated for antihypertensive drugs, furosemide and barbiturates. Arimoclomol alone or in combination had no effect on cardiovascular parameters or the antihypertensive action of enalapril, metoprolol or amlodipine.

The urinary output in SH rats, adjusted for body weight, was increased 54.4% in animals dosed with arimoclomol, 83.5% with furosemide and 143.5% with the combination of arimoclomol/ furosemide after 14 days of treatment. Beside an increase in urine output arimoclomol caused excretion of creatinine, potassium, phosphorous, uric acid and protein, whereas the combination of arimoclomol and furosemide contributed moderately to an enhancement in the excreted amounts of creatinine, potassium, phosphorous, sodium, calcium and protein.

In the presence of pentobarbital-Na (i.p.) arimoclomol (100-400 mg/kg) accelerated hypnotic onset and prolonged sleeping time. Sleeping time was doubled by 200-400 mg/kg arimoclomol, but in females treated with 400 mg/kg nearly quadrupled. Barbiturates are obsolete therapeutics in sleeping disorders. However, benzodiazepines or anti-convulsant drugs are uses in the treatment of epileptic seizures and muscle cramps especially in paediatric NPC patients. However, there was no noteworthy interaction with calcium- and sodium-channels, glutamate- and $GABA_A$ receptors observed in the secondary pharmacology screen, indicating a possible drug-drug interaction with arimoclomol unlikely.

3.2.3. Pharmacokinetics

The applicant submitted an extensive non-clinical dossier on pharmacokinetics, the extent of the submitted studies was, apart from some minor concerns that were originally raised in the D80 assessment, considered acceptable.

Analytical assay validation for quantification of pharmacokinetic and toxicokinetic endpoints in non-clinical studies (*in vitro* and *in vivo*) was conducted by different CROs for two main analytical methods: HPLC separation coupled to UV detection, and LC separation coupled to MS/MS detection. Quantification ranged from 10 to 25000 ng/mL. For detection in rat serum, an HPLC-UV method was validated by the CRO "TRC", and LC-MS/MS methods were validated by MicroConstants and CharlesRiver. Validation for arimoclomol detection in K_2EDTA plasma by LC-MS/MS was conducted by the CRO Covance, and detection in rat brain by LC-MS/MS by MicroConstants. For detection in dog serum, an HPLC-UV method was first validated by the CRO "TCR", whereas later a LC-MS/MS method was validated by MicroConstants. Finally, for embryo-foetal development studies, a LC-MS/MS method for detection in K_2EDTA plasma was validated by the CRO Covance.

The provided validation reports adequately support the analytical approaches used to analyse liquid animal specimens (and brain homogenates in the case of Report MC09B-0031) for arimoclomol (and in the case of LC-MS/MS its metabolites).

Four absorption studies were originally submitted in of the dossier at time of MAA. In the D120 responses, a fifths absorption study (Study 20ORPZP2R1GLPS588) was submitted. However, it should be noted that absorption after oral administration was also assessed in studies submitted in sections on distribution, metabolism and "other pharmacokinetic studies", and throughout the studies in the frame of toxicokinetic evaluations.

In study 0019, the pharmacokinetics of arimoclomol-associated radioactivity following oral and i.v. ^{14}C-labelled arimoclomol administration (4 mg/kg free base) was studied exclusively in male and 16 – 20-month-old Beagle dogs. Absorption in young adult male and female Wistar rats was then assessed in study 00/544-303 P, in which the pharmacokinetics after single oral and intravenous arimoclomol administration (16 mg/kg) was examined. In study C137217, the absorption and pharmacokinetics of arimoclomol (10 mg/kg) was assessed in 13-week-old male C57Bl/6J mice after p.o. and i.p. administration for up to 16 hours post-dose. Finally, in study 20ORPZP1 and 20ORPZP2R1GLPS588, the *in vitro* permeability of arimoclomol was examined in a CaCo-2 monolayer *in vitro* model.

Absorption in the investigated non-clinical species was rapid (T_{max} and C_{max} were generally attained between 0.5 – 2 h post-dose), total bioavailability after oral administration was high in rats and dogs (>75%), being in alignment with results obtained from bile cannulated animals showing complete absorption of arimoclomolrelated material (> 95%). Absorption after oral administration tended to be more rapid in female laboratory animals than in male ones, and arimoclomol exposure generally increased with increasing dose level. After repeated administration, arimoclomol exposure was in general highest on the first day of dosing compared to later time points. As the reasons for this are not apparent, a concern was originally raised on this issue (discussion further below).

In total, three distribution studies were submitted in the dossier. Note that studies evaluating distribution endpoints were also submitted (especially study 0019 and 00/544-303P), in the dossier.

In study 7027-121, tissue distribution of radioactivity was examined following administration of a single 375-mg salt/kg oral dose of radiolabelled arimoclomol to 21 male pigmented Long-Evans rats (approximately 9 weeks of age) for up to 240 hours post-dose. Similarly, in study 0018, organ, serum and tissue distribution of radiolabelled arimoclomol in male and female 6 – 8-week-old albino Wistar rats were assessed after single (i.v. and p.o.) and multiple (7-day repeated, p.o. only) administrations at 16 mg/kg (free base). The latter study also assessed foetal organ distribution in nine pregnant female Wistar rats. Furthermore, this study also assessed arimoclomol excretion in urine and faeces after single dose administration. Finally, in study BRX-345/PRE FK 002, protein binding of radiolabelled arimoclomol in human, dog and rat serum was studied at 0.4-16 µM. Accumulation of arimoclomol was observed in rats on day 7 in Study No. 0018 and is explained by a possibly longer half-life of arimoclomol metabolites. Exposure ratios of the primary plasma metabolites M2 and M105 in rats and

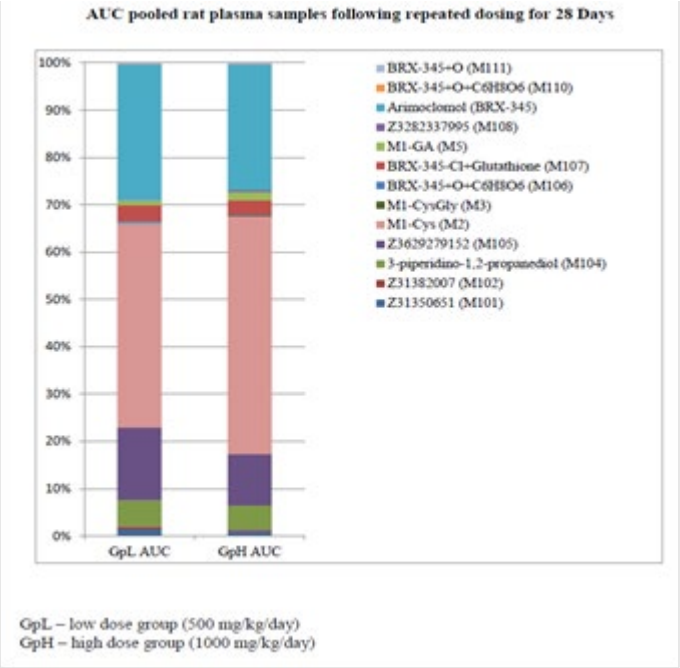
humans at steady state have been previously shown to be adequate. Suspicious accumulation of arimoclomol or its metabolites has not been confirmed in clinical trials.

Arimoclomol exhibited low binding to plasma proteins (maximally 10%).

Calculated volume of distributions were high, ranging from 1.50 L/kg in male Beagle dogs (at a dose of 4 mg/kg after i.v. administration) to 8.59 L/kg in male and female rats (at a dose of 25.8 mg/kg after i.v. administration). These values are in a range indicating distribution throughout the total body water content, whereas they are not high enough that strong accumulation in body fat can be anticipated.

Arimoclomol-related material (arimoclomol and its metabolites) was rapidly and widely distributed in laboratory animals. As can be predicted by the moderately high volume of distribution, exposure to arimoclomol was higher in tissues than in plasma: organ:plasma ratios of arimoclomol-material associated radioactivity in the rat biodistribution studies 7027-121 and 0018 were generally (considerably) higher than 1. Elimination kinetics of arimoclomol from blood is biphasic: Throughout the submitted non-clinical studies, rapid initial elimination kinetics were noted immediately post-dose, amounting to short mean plasma half-lifes of arimoclomol in rats (1.5 hours), rabbits (1 hour) and dogs (1.3 hours). (Note that plasma elimination half-life of arimoclomol was somewhat higher in humans (3-4.5 hours) than in animals). In this first elimination phase, the vast majority of administered arimoclomol was cleared from blood, e.g. in dog study 7027-122 in which ~80 to 90% of arimoclomol-associated radioactivity was eliminated from blood with a mean half-life of 2 to 4h. The rapid initial elimination from plasma was presumably caused by a.) the high volume of distribution of arimoclomol that causes fast partitioning to tissues; b.) rapid renal excretion of arimoclomol, which is partly governed by active tubular secretion (discussed further below); and c.) rapid turnover of arimoclomol into metabolites. The subsequent second phase of the biphasic elimination kinetics was however determined by strikingly slower half-lifes that were more than an order of magnitude higher than the one of arimoclomol. For example, in rat study 0019, plasma half-lifes during the second elimination phase were 90 hours (p.o.) and 80 hours (i.v.). In another rat biodistribution study, most investigated tissues retained quantifiable radioactivity up to 240 hours post-dose (Study 7027-121). Similarly, in dogs, 10 to 20% of the administered arimoclomol-related radioactivity eliminated from plasma only with a mean half-life of approximately 140 to 180 hours (Study 7027-124). The applicant speculates that the slow second phase plasma elimination and overall excretion kinetics were caused by retention of arimoclomol metabolites in the cellular compartment and/or enterohepatic circulation.

Because of the rapid plasma elimination half-life of arimoclomol in the first phase of the biphasic elimination process, no accumulation of arimoclomol itself was observed in laboratory animals. However, because of the strikingly slower second-phase elimination kinetics of arimoclomol-related metabolites, it can be expected that the metabolites develop considerably higher steady-state exposures during chronic daily dosing than after single dose administration. This assumption was supported by rat study 8384372, in which after 28 days of chronic daily dosing, exposure to arimoclomol-related material was approximately twice as high as after single administration. This absolute increase in arimoclomol-related material was caused by an increased retention of metabolites at chronic dosing, whereby plasma levels of the metabolite M2 even exceeded the ones of arimoclomol, and plasma levels of the metabolite M105 approximately reached a quarter of the ones of arimoclomol (as demonstrated in the Figure below):



In agreement with the results of study 8384372, detected signals in organs and tissues were considerably increased (4-12-fold) in the whole radio autography study 0018 after 7 days of dosing when compared to signals after the first day of dosing. As M2 and M105 potentially harbour safety relevant concerns (hERG inhibition), the accumulation of arimoclomol-related metabolites is of potential safety relevance.

In rats, arimoclomol related radioactivity exhibited a strong tendency to accumulate in melanin-containing tissues, whereby accumulation in eyes appeared to be drastically higher than in pigmented skin. For example, at 240 hours post-dose in biodistribution study 7027-121 (in which pigmented Long-Evans rats were used), the by far highest arimoclomol related radioactivity was detected in eyes, (72.0, 5.03, 3.04, 2.95, and 2.56 µg equivalents ^{14}C-BRX-345/g were measured in eyes, thyroid, liver, heart, and kidneys, respectively). The high eye concentration at 240 hours post-dose in this study represented an eye:plasma ratio of 261! Note that in the biodistribution study 0018 (in which albino Wistar rats were used), eyes were among the organs exhibiting particularly low arimoclomol related radioactivity, presumably because of the low pigmentation of the rat strain used in this study. This notable difference between both rat biodistribution studies further demonstrates the strong binding and subsequent accumulation of arimoclomol to pigmented tissues such as the eyes.

Arimoclomol-related radioactivity and arimoclomol (detected by LC-MS/MS) was detected in rat brains, whereby amounts in brain were per mass unit lower than in blood. In rat brains, arimoclomol-related radioactivity was detected up to 240 hours post-dose (latest sampling point). Similarly, intact arimoclomol was also demonstrated in cerebrospinal fluid and brain in dogs and mice (studies C137217 and 05/982-090K). In study 0018, the applicant demonstrated that after single administration of radiolabelled arimoclomol, radioactivity penetrated the placenta, and was found in foetal tissues at an exposure level comparable to that in the dam. In the same study, foetal brain arimoclomol concentrations even proved to be higher than maternal brain concentrations.

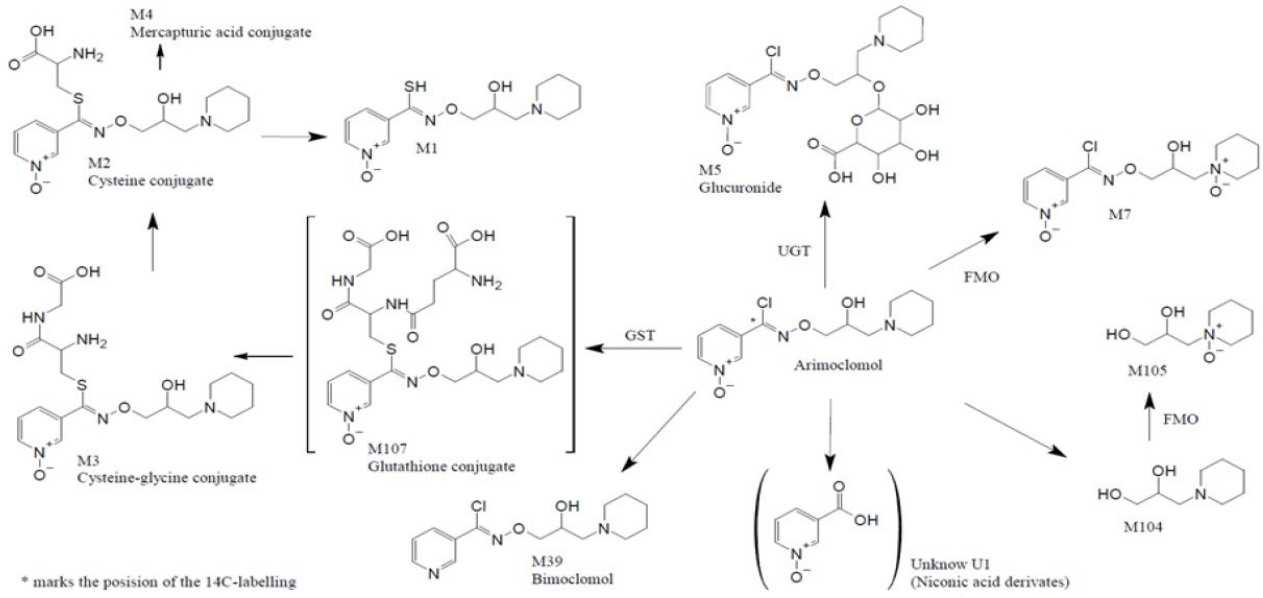
Arimoclomol AUC was mostly linearly proportional to increasing dose levels. No strong gender differences were noted in the distribution of arimoclomol and arimoclomol-related material.

In total, ten studies on metabolism were submitted in the dossier.

Study 7027-130 strived to identify whether human cytochrome P450 isoenzymes are involved in the *in vitro* metabolism of radiolabelled arimoclomol in human microsomes (NADPH used as cofactor). *In vivo*

metabolism (as well as absorption and excretion) of radiolabelled arimoclomol after oral administration (375 mg/kg salt) was then studied in intact and bile duct cannulated 6 to 9 weeks old male rats (Study 7027-122). Similarly, absorption, metabolism and excretion of radiolabelled arimoclomol was studied after oral administration (70 mg/kg) in intact and bile duct cannulated female and male Beagle dogs (Study 7027-124). Then, in the early study BRX-345 PRE SK-006, metabolites from rat and human specimens were identified and characterised based on liquid chromatographic separation coupled to mass spectroscopy. In the later study 287N-0801 part 2, metabolites were identified and profiled in plasma, urine and faeces after oral administration of radiolabelled arimoclomol (2500 mg/kg) to male CD-1 mice (specimens were collected from study 287N-0801 part 1). Subsequently, in study XT194101, the applicant investigated which (recombinant) UDP-glucuronosyltransferases are involved in the *in vitro* turnover of arimoclomol into the glucuronic acid conjugate metabolite M5 in human microsomes. In study XT194103, the applicant attempted to investigate the metabolic pathways converting arimoclomol to the important cleavage product metabolite M105 in human microsomes (NADPH as cofactor), especially emphasising on the role of (recombinant) flavin-containing monooxygenases (FMO). Later, in study 8384372, absorption and metabolism of radiolabelled arimoclomol (375 mg/kg) after oral gavage administration was studied in male rats. Furthermore, metabolism and speciation of arimoclomol-related material in plasma after repeated dose administration (for 28 days, specimens obtained from the rat fertility study 8376167), was also assessed in this study. Also, human metabolism studies were submitted in the dossier. In study 8393986, the applicant characterised the plasma metabolites of arimoclomol after repeated administration for up to six days (at 400 mg thrice a day, at 8 h dose intervals) by LC-MS/MS at steady-state (samples obtained from clinical study 180308-CS030, sponsor reference: OR ARI-MET-01). In data report 8412783, additional data to study 8393986 was presented.

Phase I metabolism of arimoclomol by CYP450 monooxygenases was inefficient, only the isoforms 1A2 and, more extensively, 2D6 were demonstrated to metabolise arimoclomol, but CYP450-mediated metabolism was quantitatively negligible to other turnover routes. Arimoclomol is metabolised by several routes, as demonstrated in the Figure below:



Primary routes of arimoclomol metabolism are a.) de-chlorination with subsequent glutathione conjugation and derivatisation of the conjugate moiety; b.) O-glucuronidation; and c.) NO-cleavage. The most abundant metabolites produced by these reactions at steady state in animals and humans are M2 (cysteine conjugate), M5 (O-glucuronide) and M105 (cleavage product). The applicant

demonstrated that different UDP-glucuronosyl transferase isoforms (specifically UGT1A3, 1A9, 2B4, 2B7 and 2B17) can transform arimoclomol to M5 in human microsomes *in vitro*. The exact molecular mechanisms behind the NO-cleavage were not determined; however, FMO1 and FMO3 were demonstrated *in vitro* to potentially form M105 out of the intermediate 104 (and M109 out of arimoclomol). The applicant did however not succeed to elucidate the metabolic pathways leading to M104. Metabolism was very similar between the tested non-clinical species and humans. The main metabolites in human plasma (>10%: M2, M5 and M105) were sufficiently present during non-clinical animal studies; their safety profile can therefore be considered as qualified.

As discussed before, the speciation of arimoclomol-related material in plasma is different after chronic administration as compared to after single administration, whereby the fraction of arimoclomol metabolites of the total plasma amount of arimoclomol-related material considerably increases after chronic administration (because of their slower elimination kinetics).

No excretion study was submitted, as excretion has already been sufficiently assessed in other sections of the submitted dossier.

In most rat and dog studies, renal excretion in urine amounted to approximately 60% of the administered dose (in mice urinary excretion was only 50%). Faecal excretion of administered dose was roughly between 20 and 30% in rats and dogs (and only 8 % in mice). Biliary excretion amounted to approximately the same extent as faecal excretion in bile-cannulated rats and dogs (Study 7027-122 and 7027-124, respectively). In comparison to rats and dogs, urinary excretion was higher in humans (77.5%), whereas faecal excretion was less important than in these animals (only 12% in humans). In urine, unchanged arimoclomol constituted the by far largest contribution to excreted arimoclomol-related material, whereas in faeces, metabolites of arimoclomol largely prevailed.

In total, eleven non-clinical pharmacokinetic drug interaction studies were submitted in the dossier.

In study XT198104, the potential of M2 to inhibit ABC (ATP-binding cassette transporter, specifically MDR1 and BCRP) and SLC (solute carrier, specifically OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K) transporters was assessed in different *in vitro* (mostly cDNA transfected) cell models. Similarly, in study XT208069, the applicant investigated in purified plasma membranes isolated from an insect cell system (Sf9 cells transfected with baculovirus) whether arimoclomol inhibits the transporter BSEP (bile salt export pump). Then, in study XT193101, the applicant assessed whether arimoclomol induces the cytochrome 450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in primary human hepatocytes. The same objective was evaluated in the older study 7027-123. Subsequently, in study 8300495, the applicant assessed whether arimoclomol inhibits the enzymatic action of the CYP450 isoform 2C8 (in a human liver microsome *in vitro* assay). In the broad study XT195105, the applicant assessed whether arimoclomol and M2 inhibit the enzymatic activity of the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes (NADPH added as cofactor). The same objective was evaluated in the older study 7027-131. Finally, in study XT198103, the applicant studied the ABC (MDR1 and BCRP) inhibition potential of arimoclomol, whereas the applicant studied the interaction of arimoclomol with the human SLC transporters OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 in study CYP0882_R1, and MATE1 and MATE2-K in study CYP0882-R2-001 and CYP0882-R2-002 (all these studies were mostly conducted with cDNA transfected cells).

In these studies, arimoclomol was identified to be a substrate of the renal efflux transporters MATE1 and MATE2-K, and an inhibitor of OCT2. The applicant assessed the potential of arimoclomol-related material for pharmacokinetic drug interactions in a victim drug and perpetrator drug assessment. Regarding the former, the applicant concludes that arimoclomol is not a substrate of the P-gp, BCRP, OAT1, OAT3 and OCT2 transporters, and that the potential risk for drug interactions is considered low since arimoclomol is metabolised via several routes and since no MATE inhibitors have been identified

as clinically relevant co-medications in the NPC population. Regarding arimoclomol as potential perpetrator drug, the applicant concluded that arimoclomol is not predicted to cause clinically relevant direct, time- or metabolism dependent inhibition or induction of CYP450 enzymes and is further predicted not to inhibit the ABC and SLC transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1 and MATE2-K. Reference to cut-off value suggested by FDA for MATE transporter inhibition is made and is considered to be acceptable. EMA guideline on the investigation of drug interactions has not been updated since 2013 (EMA, 2013) and therefore is considered obsolete comparing to FDA guideline that has been updated in 2020 (FDA, 2020a) including the scientific knowledge recently obtained regarding the MATE inhibition (Lee et al. 2017). The potential inhibition of OCT2 at clinically relevant levels is appropriately mentioned in the SmPC. No potential drug interactions (as perpetrator) were predicted for M2. No interaction studies were carried out for M5 and M105 (the other metabolites in humans at >10% plasma concentration); and no CYP26D induction assessment was conducted.

Finally, the applicant submitted two other pharmacokinetic studies: In study 05/099-303P:6, pharmacokinetics were evaluated during 6 months of chronic arimoclomol administration to CRL:(WI) BR rats at 200, 400 and 900 mg/kg bw/day. In study 05/982-090K, pharmacokinetics after 14 days of b.i.d. arimoclomol dosing (2x 80 mg/kg bw per day, with 6-hour intervals between the administration times) was assessed in Beagle dogs. The evaluated pharmacokinetic endpoints in these studies were in good correlation with the remainder of the submitted studies.

3.2.4. Toxicology

The applicant submitted an extensive non-clinical toxicology dossier. Originally, one major objection and several other concerns were raised on toxicological aspects. However, all concerns were successfully resolved by the applicant during the marketing authorisation application procedure.

In total, six single dose toxicity studies were submitted. Three of these early studies (early 2000's) were conducted with mice (NMRI strain) by administering arimoclomol orally (Study 00/544-001E), intravenously (Study 00/544-011E) and intraperitoneally (Study 00/544-003E). The same experimental programme was also conducted with Wistar rats (oral, intravenous and intraperitoneal administration, Studies 00/544-001P, 00/544-011P and 00/544-003P, respectively). In oral single dose toxicity studies doses up to 5000 mg/kg/day in mice and up to 5700 mg/kg in rats were used, in repeat-dose study 1311-002 daily doses up to 3600 mg/kg/day were used in rats. Discussion related to high dose selection which clearly exceeded the MTD for single-dose studies and repeat-dose study No. 1311-002 was provided by the applicant.

LD_{50} values obtained in mice were >5000 mg/kg (p.o.), 250 mg/kg (i.v.) and 1100 mg/kg (i.p.) (all doses in respect to the citrate arimoclomol formulation). In rats, the obtained LD_{50} values were 2600 mg/kg (p.o.), 300 mg/kg (i.v.) and 800 mg/kg (i.p.) (citrate formulation). The applicant stated that the cause of the observed mortalities in mice and rats was circulatory insufficiency; however, no detailed discussion on the pathogenesis of the observed circulatory failures at lethal arimoclomol administration was provided. Note that after intravenous administration of a lethal dose, the animals died within seconds to a few minutes. However, after intraperitoneal administration of a lethal dose, death occurred within minutes to some hours post-dose, and after oral administration, the animals died after hours to maximally two days post-dose.

Repeated dose toxicity was evaluated in young adult rats and in Beagle dogs; in total eight studies were submitted.

In the rat study 1311-002, repeated dose toxicity was assessed for two weeks in male and female Sprague Dawely rats at a q.d. and b.i.d. dosing regimen at doses up to 3600 mg/kg bw/day (citrate

formulation). Then, in study 00/544-100P, repeated dose toxicity was studied in male and female Wistar rats for 4 weeks at a q.d. dosing schedule at doses up to 1500 mg/kg bw/day (citrate formulation); recovery was studied for 2 weeks after the last dose was administered. Finally, repeated dose toxicity was assessed in study 00/544-107P for six months in male and female Wistar rats (including a 4-week recovery period) at a q.d dosing schedule up to 900 mg/kg bw/day (citrate formulation). In this pivotal rat repeated dose toxicity study, 20 animals were used per dose group and sex, and 12 animals in each respective recovery group.

Repeated dose toxicity was initially studied for 14 days in male and female dogs in study 00/544-028K at 210 mg/kg bw/day (citrate formulation) at a q.d. dosing schedule. Then, repeated dose toxicity in male and female dogs was again assessed for 14 consecutive days of arimoclomol administration (up to 320 mg/kg bw/day, citrate formulation), but on a q.d. and b.i.d. dosing schedule (Study 1311-003). Subsequently, the applicant assessed repeated dose toxicity for 28 days of consecutive arimoclomol dosing (up to 219 mg/kg bw/day, citrate formulation) in male and female dogs in study 00/544-100K (q.d. administration). Repeated dose toxicity of arimoclomol (up to 160 mg/kg bw/day citrate formulation, q.d. dosing schedule) was then studied in male and female dogs in study 00/544-107K for 3 months. This is the only study in which recovery from the observed adverse effects was assessed in dogs (in this case in the control and high dose group, but only at n = 2 animals per sex). Finally, in the pivotal repeated dose toxicity study, male and female dogs were administered arimoclomol up to 160 mg/kg bw/day (citrate formulation) at a q.d. and b.i.d. dosing schedule for 26 and 52 weeks (Study 05/982-201K). No recovery groups were included in this pivotal dog repeated dose toxicity study. Note that the group sizes throughout the dog studies were small and maximally amounted to n = 4 per dose group and sex.

A pattern of certain toxicological off-target adverse effects was frequently observed throughout the submitted rat and dog repeated dose toxicity studies. The lowest NOAEL observed in rat studies was 200 mg/kg bw/day (Study 00/544-107P), and the lowest one in dogs was 50 mg/kg bw/day in both studies 00/544-107K and 05/982-201K. At high doses (above the respective maximum tolerable doses (MTD)), arimoclomol administration was associated with mortality (mostly, the causes of death could not be elucidated) and/or severe clinical signs. The latter were comprised by neurological signs such as reduced activity, ataxia, dyspnoea, and tremors. Furthermore, arimoclomol administration at intermediate and high doses frequently resulted in body weight decreases, body weight gain decreases, decreased food consumption, and thin appearance of the animals. The applicant speculates that the arimoclomol-related decreases in body weight subsequently induced secondary effects, ranging from decreased organ weights to delayed sexual maturation. In addition, clinical observations related to gastrointestinal adverse effects were frequently observed in animals of intermediate and high arimoclomol groups, ranging from abnormal faeces and emesis to diarrhoea. The applicant summarises that the exposure ratios between human exposure and exposures at dose levels with mortality/severe clinical signs leading to euthanasia were at least nine, human risk is therefore claimed to be low.

In study 00/544-107K tremor and reduced activity was observed at all dose levels. Tremor has been identified as an adverse reaction in humans and is listed in the SmPC. Although the clinical significance of the observed reduced activity in dogs cannot be fully excluded, a causal relationship of arimoclomol with adverse events of lethargy has not been established in clinical studies.

In addition to these clinical signs, characteristic haematological alterations were frequently observed at generally high and/or intermediate arimoclomol doses, ranging from alterations in erythrocyte endpoints (mostly e.g. decreases in erythrocyte counts, decreases in haematocrit, decreased haemoglobin, but frequently increases in reticulocytes) from alterations of leucocyte endpoints (mostly e.g. decreases in peripheral lymphocytes and granulocytes, and frequently increases of neutrophils). Coagulation endpoints were only inconsistently altered across the conducted animal studies.

Urinalysis investigations sometimes demonstrated arimoclomol-related increased urinary volume, increased specific gravity and decreased urinary pH; however, these findings were not consistently observed throughout the submitted toxicology studies.

Clinical chemistry investigations frequently demonstrated arimoclomol-related increases in cholesterol, bilirubin, phosphate values, and decreases in glucose, alkaline phosphatase, urea, creatinine, sodium and chloride values in relation to control groups. The increases in cholesterol and decreases in glucose and urea were the most common clinical chemistry alterations of the submitted toxicity studies, at magnitudes that indicate that these alterations are clearly based on a test-article related effect.

In correlation with the observed arimoclomol-related alterations of differential leucocyte counts, necrosis in lymphoid organs, lymphoid and bone marrow depletion, and reduced weight and/or atrophy of lymphoid organs (mainly thymus and spleen, but also lymph nodes) were observed. The applicant hypothesised that these arimoclomol-related effects could mainly be the result of a stress response, or be secondary to the arimoclomol-related decreases in body weight, but also notes that a direct test-article related effect on the immune system cannot be excluded. In this context, also note that arimoclomol doses above the MTD occasionally induced infection of the upper gastrointestinal tract by opportunistic pathogens, as observed in the rat study 1311-004. This could demonstrate that a certain extent of immunosuppression occurs at high supra-therapeutic arimoclomol doses. However, the applicant stated that adverse effects to the immune system were exclusively observed in animal studies, and at least at a 9-fold exposure above the clinical exposure. Furthermore, the applicant stated that no indications of immunosuppressive effects induced by arimoclomol were observed in the clinical trials. To conclude, the non-clinical toxicology studies indicate a risk potential of arimoclomol-mediated immunotoxicity; however, the clinical relevance of this aspect is uncertain.

Apart from the immune system, target organ toxicity in the submitted studies was also observed for the liver, kidney, the reproductive organs (discussed under "reproductive and developmental toxicity" further below), the gastrointestinal tract and sporadically the eyes (discussed later under "other toxicity studies").

In regard to the arimoclomol-related off-target hepatic toxicity, increased liver weights were consistently observed in both rats and dogs across the submitted studies. Occasionally, this was accompanied by panlobular hepatocyte hypertrophy and relevant clinical chemistry changes, mainly increased bilirubin and cholesterol. Transaminases were only rarely increased in toxicity studies (in fact, they were more frequently decreased than increased). Sporadically, also hepatic necrosis was observed at high arimoclomol doses. Finally, in short time toxicity studies in dogs, vacuolar degeneration of the liver was observed together with decreased glycogen levels and proliferation of cells of the mononuclear phagocyte system. The applicant speculates that the observed hepatic alterations could have been partly caused by a compensatory mechanism due to excessive xenobiotic metabolism after administration of high arimoclomol doses, and in the case of vacuolar degeneration and decreased glycogen because of arimoclomol-related decreases in body weight. An effect of increased xenobiotic metabolism could potentially be supported by the occasionally observed increased thyroid weights and follicular cell hypertrophy. However, the applicant considered the hepatic alterations adverse when e.g. hepatic clinical chemistry changes and/or liver necrosis accompanied the liver weight changes. This interpretation is supported.

Renal toxicity was primarily observed in the 26-week rat study, in which increased incidences of chronic nephropathy were observed at 2- to 5-fold the human exposure. These adverse effects were accompanied by proteinuria, pale kidneys and increased kidney weights. The applicant considered these effects adverse. It is uncertain whether these observations can be correlated with occasionally observed arimoclomol-related increased urinary volume, increased specific gravity and decreased urinary pH. Limited clinical data provided by the applicant shows possible arimoclomol treatment

related renal toxicity and acute renal failure is classified as an important potential risk in the Risk Management Plan.

As mentioned before, clinical signs such as diarrhoea and abnormal faeces at intermediate and high doses indicated an adverse effect of arimoclomol on the gastrointestinal tract (GIT). Indeed, administration of high doses of arimoclomol induced local irritation of the GIT. Microscopically, hyperkeratosis and epithelial hyperplasia in the non-glandular stomach were observed together with inflammation and erosion/ulceration in the non-glandular and glandular stomach and duodenum in rats. In dogs, glandular dilatation, inflammation and haemorrhage was observed throughout the gastrointestinal tract in several animals. The applicant notes that these effects were generally only observed at mid and high dose levels. However, the applicant concluded that the frequency of vomiting and diarrhoea was higher in arimoclomol than placebo groups in clinical trials, potentially indicating that the observations in laboratory animals can to a certain extent be translated to patients.

Finally, characteristic alterations were observed in recorded ECGs of dogs exposed to arimoclomol. In the two weeks dog study 1311-003, ECG revealed a slight (~ 10%) increase in QTc interval by the end of the dosing period at the highest dose level of 160 mg/kg arimoclomol citrate b.i.d., i.e. at an exposure corresponding to 28-fold the human exposure of arimoclomol (based on C_{max}). This observation could be clinically relevant as safety pharmacology studies demonstrated that the three most important human metabolites M2, M5 and M105 as well as arimoclomol inhibit the hERG channel (more detailed information in the discussion on safety pharmacology). The applicant concluded that a direct effect of arimoclomol on the observed QT prolongation in dogs cannot be excluded, but further mentions that because of sufficiently high safety factors in the clinical use, the risk to patients is probably low. Of note, the applicant conducted a QT trial in healthy volunteers, which revealed no adverse effects of arimoclomol on the ECG of healthy volunteers at supratherapeutic dose (Study OR-ARI-TQT-01). In addition to QT prolongations, p wave amplitudes were frequently decreased in dogs exposed to arimoclomol. Furthermore, QRS complex amplitudes were frequently increased, and the duration of the QRS complex was frequently prolonged. Furthermore, in the dog study 00/544-107K, heart weights were decreased. At MAA, the applicant did not sufficiently discuss these cardiologic findings in arimoclomol-exposed dogs; a concern was therefore originally raised on this issue (see below).

The applicant submitted a standard battery of genotoxicity studies. At MAA, in total, eight empirical genotoxicity studies were conducted. In regard to the most important metabolites at steady state (M2, M5 and M105), mutagenicity was originally not empirically assessed at MAA. However, in silico genotoxicity predictions of these metabolites were submitted in the dossier.

In studies 7027-126 and 00/544-007M, the potential mutagenicity of arimoclomol was studied by means of the bacterial reverse mutation assay (Ames test). Mutagenicity of arimoclomol was further studied in a mouse lymphoma forward mutation assay (Study 7027-138). *In vitro* chromosomal aberration by arimoclomol was assessed in study 7027-125 and 00/544-020C in Chinese hamster ovary cells. *In vivo* genotoxicity (specifically clastogenicity and aneugenicity) of arimoclomol was assessed in mouse bone marrow mirconuceus assays (Study 7027-139 and 00/544-013E) as well as in a Wistar Han rat *in vivo* micronucleus study (Study BN28JX).

All submitted *in vitro* and *in vivo* genotoxicity studies demonstrated that arimoclomol was non-genotoxic at the applied test conditions. In regard to the metabolites (especially relevant in this context are M2 and M105), the evaluation of the potential clastogenicity and aneugenicity was presumably covered in the *in vivo* micronucleus studies. However, at time of MAA, mutagenicity of these metabolites was not empirically assessed. The lacking empirical mutagenicity assessment of the metabolites was substantiated by a.) the lacking capability of *in vivo* micronucleus assays to detect mutagenicity; and b.) the lack of adequate metabolic activation of arimoclomol in the conducted *in*

vitro mutagenicity assays (arimoclomol is not metabolised by phase 1 reactions; however, only phase 1 simulating S9 with NADPH regenerating system was added to the Ames and mouse lymphoma forward mutation assays). To estimate the potential mutagenicity of M2, M5 and M105, the applicant conducted in silico and read across assessments. However, this was not considered sufficient to reliably determine the mutagenicity of these qualitatively important metabolites. A major objection was originally raised on this issue. However, in the D120 responses, the applicant submitted Ames tests of M2 and M105 (Study No. 8468128 and Study No. 8468125, respectively) which proved that both metabolites are non-mutagenic in the bacterial reverse mutation assay. Therefore, the major objection was resolved.

No carcinogenicity studies were submitted at MAA; the applicant however submitted a 26-week carcinogenicity transgenic rasH2 mouse study (Study 8432745, b.i.d. administration) with the D120 responses, and is committed to submit a 104-week rat carcinogenicity study (Study PQ64LW, q.d. administration) as a post-marketing measure in August 2022. The latter was agreed by CHMP in the protocol assistance procedure EMEA/H/SA/3709/1/2017/PA/SME/III.

However, at this point, it was noted that arimoclomol could be a non-genotoxic carcinogen, as it induces heat shock proteins, which are thought to play significant roles in the molecular mechanisms leading to cancer development and metastasis (Wu et al. 2016; DOI: 10.1016/j.tips.2016.11.009). Nevertheless, in the 26-week carcinogenicity transgenic rasH2 mouse study (Study 8432745), no relevant signs of arimoclomol-induced carcinogenicity were identified. Note that the percentage of haemangioma (6.7%) at 750 mg/kg arimoclomol b.i.d. was slightly above the historical background range of 0 to 4% (but the statistical analysis did not reveal a significant difference in tumour distribution among groups). However, as haemangioma and haemangiosarcoma are common malignancies in rodents, but exceedingly uncommon in humans, and as the incidence of both neoplasms combined at 750 mg/kg b.i.d. was inside the historical background range of 0-12%, no concern was raised on this finding. Nonetheless, the applicant wasrecommended to especially screen for haemangiomas and haemangiosarcomas in the to-be-submitted 2-year rat carcinogenicity study in order to test whether the signal found in the rasH2 mouse study SK86RN can be reproduced in rats.

In total, ten studies were submitted to assess the potential reproductive and developmental toxicity of arimoclomol. In study 8376167, the applicant assessed the effects of arimoclomol (up to 1000 mg/kg bw/day citrate formulation) on fertility and/or early embryonic development in male and female Wistar rats (n = 20 per group and sex) at a q.d. dosing schedule. Then, embryo-foetal development (EFD) was preliminarily studied in Wistar rats at a q.d. dosing schedule (Study 8376181) up to 1000 mg/kg bw/day (citrate formulation), and at a t.i.d. dosing schedule up to 1500 mg/kg bw/day (citrate formulation) (Study JJ73QP). The pivotal EFD Wistar rat study 8376160 (n = 20 per dose group) was conducted at a q.d. dosing regimen up to 1000 mg/kg bw/day (citrate formulation). However, also a second pivotal Wistar rat EFD study was submitted (Study VR31MQ) in which the potential effects of arimoclomol on EFD were studied at a t.i.d. dosing schedule up to 1000 mg/kg bw/day (also at n = 20 per dose group).

In addition, EFD toxicity was studied in rabbits, representing a non-rodent species: A dose-range finding EFD study (Study 8376158) was conducted with NZW rabbits up to 275 mg/kg bw/day (citrate formulation) at a q.d. dosing schedule. In the subsequent pivotal NZW rabbit study (n = 20 per dose group), effects of arimoclomol on EFD were assessed up to 200 mg/kg bw/day (citrate formulation), also at a q.d. dosing schedule.

The potential effects of arimoclomol on peri- and postnatal development were assessed in Wistar rats in Study 8376159 (n = 22 F0 dams per dose group) up to 1000 mg/kg bw/day at a q.d. dosing schedule.

Finally, two juvenile rat toxicity studies were submitted. In the first dose-range finding study 497448, the applicant assessed the juvenile toxicity of arimoclomol when administered to Sprague Dawley rats up to 400 mg/kg bw/day from Day 21 post partum until 6 weeks of age (q.d. dosing schedule). In the pivotal study, juvenile toxicity (including recovery from observed adverse effects) was investigated in the Wistar rat study 8345287, in which arimoclomol was administered up to 1000 mg/kg bw/day either from day 7 to 21 post partum, or from day 7 to 63 post partum (at a q.d. dosing schedule).

Arimoclomol induced adverse effects on male reproductive organs at ≥900 or 1000 mg/kg/day (citrate formulation), corresponding to ≥10- or 5-fold the human exposure, whereby decreased weight or small size of epididymides and testes, accompanied by oligospermia in epididymides and atrophy of the germinal layers in testes was observed. Furthermore, a reduction in male fertility and reduced sperm motility, immotile sperm, reduced sperm count, and increased sperm abnormalities were observed in the fertility study 8376167. Note that toxicity to the male reproductive tract was also observed in rat and dog repeated dose toxicity studies. Similarly, arimoclomol affected female fertility and early embryonic development. In study 8376167, the number of corpora lutea was decreased in test-article group females, and the fertility and the fecundity index of female rats at arimoclomol citrate exposure of 1000 mg/kg/day was decreased (corresponding to 5-fold the human exposure). Additionally, an increased pre-implantation loss was noted in test article females. The applicant summarised that a relevance of these adverse effects on fertility, as observed in laboratory animals, cannot be excluded for patients.

Arimoclomol proved to be toxic to embryo-foetal development, both in rats and rabbits. In the submitted EFD studies, increased pre- and postimplantation losses, including total litter losses, were observed at exposures down to 3- and 5-fold the human exposure, respectively. Furthermore, decreased placental and foetal weights, foetal skeletal variations and malformations affecting the brain ventricles (domed cranium, hydrocephaly, and cranial meningocele accompanied by dilated brain ventricles, cerebral and cerebellar haemorrhages, bipartite supraoccipital, and marked enlargement of the anterior and posterior fontanelles) were observed in animals of test-article groups. Because of these observations, the applicant issued a contraindication on pregnancy in the SmPC (section 4.6).

In the PPND study, the offspring from rat dams administered 1000 mg/kg/day had continuously lower body weight and food consumption (F1 females only). In view of the total *in utero* losses and effects on offspring body weight at 1000 mg/kg/day, the NOAEL was considered to be 750 mg/kg/day both for the maternal animals and the pre-and post-natal development of subsequent offspring.

Finally, juvenile toxicity proved to be similar to adult toxicity, as established in repeated dose toxicity studies. However, in the pivotal juvenile toxicity study 8345287, macroscopic and microscopic renal pelvic dilatations were observed in both sexes at all doses. However, as this is a common finding when juvenile rats are administered excessive amounts of xenobiotics, the applicant concluded that this finding is probably not clinically relevant. Furthermore, a delay in sexual maturation was observed in both males and females. However, the applicant associated this finding with the generally decreased body weights of animals administered high amounts of arimoclomol. This appears plausible.

According to the guideline ICH S11 on nonclinical safety testing in support of development of paediatric pharmaceuticals section 3. "Design of nonclinical juvenile animal studies" toxicokinetics assessment should consider both pharmaceutical ingredient and relevant major human metabolites. Major human metabolites were not assessed in juvenile animal studies as at the time of the conduct of the two juvenile toxicity studies, M2, M5 and M105 were not yet identified as the most abundant human metabolites. No additional separate non-clinical toxicokinetics data in juvenile animals are considered necessary since toxicokinetics of these metabolites is assessed in other non-clinical studies submitted by the applicant and juvenile toxicity proved to be similar to adult toxicity.

Three older (early 2000s) local tolerance studies were submitted. At first, acute skin sensitisation of arimoclomol was evaluated on guinea pig skin of 10 animals by the Magnusson and Kligman method (Study 00/544-104T). Then, acute skin irritation of arimoclomol was evaluated in three NZW rabbits by the Draize method (OECD 404) (Study 00/544-006N). Finally, acute eye irritation was also studied in three NZW rabbits by the Daize method (OECD 405) (Study 00/544-00SN).

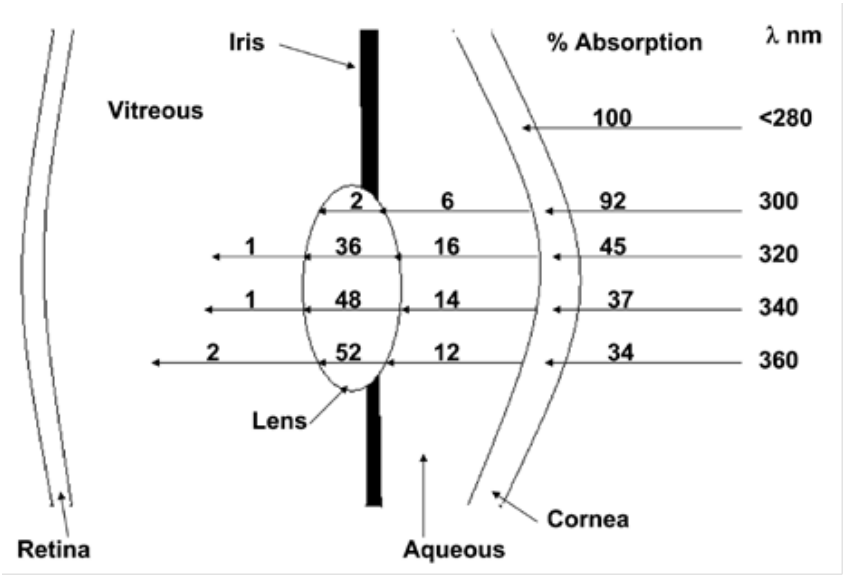
In these studies, arimoclomol was determined to be a moderate skin sensitiser, non-irritating to skin, and slightly irritating to eyes.

No dedicated antigenicity and immunotoxicity studies were conducted. However, antigenicity of arimoclomol was anticipated in the skin sensitisation study 00/544-104T, and immunotoxicity was anticipated at intermediate and high doses in repeated dose toxicity studies.

No dependence studies were conducted. However, the applicant concluded that the abuse potential of arimoclomol is negligible.

No studies on impurities were submitted in module 4 of this dossier.

Originally, no phototoxicity study was submitted in the dossier. However, the applicant reported that the molar extinction coefficient of arimoclomol in the relevant range of natural sunlight (290-700nm) is 3602 L/mol*cm, therefore, it could be expected to be sufficiently photoreactive (ICH S10). Furthermore, the applicant stated that arimoclomol mainly absorbs UVB with wavelengths around 300 nm. UVB is mainly absorbed in the epidermis, and some UVB may reach the dermis (D'Orazio et al, 2013; DOI: 10.3390/ijms140612222). It was therefore considered possible that vulnerable stem cells at the bottom of the epidermis may be susceptible to a potential phototoxic damage by arimoclomol. Additionally, the applicant did originally not discuss potential phototoxicity of arimoclomol in the eyes. As mentioned before, arimoclomol mainly absorbs UVB with wavelengths around 300 nm. Approximately 2% of UVB light of this wavelength reaches the eye lenses (Lucas RM 2011, doi: 10.1097/ICL.0b013e31821cb0cf), as represented in the Figure below taken from this publication:



It was therefore considered possible that arimoclomol could act as a phototoxicant in anterior tissues of the eye. As arimoclomol accumulates both in skin and eyes, a concern was originally formulated on this aspect. However, with the responses to the D180 outstanding concerns, the applicant submitted a GLP-compliant 3T3 fibroblast neutral red uptake phototoxicity assay (Study 20315652). No toxicity was observed in this study up to a concentration of 100 µg/mL, both in the presence and absence of irradiation. Therefore, the applicant classified arimoclomol as non-phototoxic. Importantly, in this

neutral red uptake 3T3 fibroblast study, irradiation was guaranteed also at the absorption maximum of arimoclomol (in the UVB wavelength field at approximately 300 nm).

Finally, the applicant submitted two combinatory repeated dose toxicity studies in the submitted dossier. In both studies, the combinatory toxicity of arimoclomol and riluzole was assessed. Riluzole is a medication for the treatment of amyotrophic lateral sclerosis, for which arimoclomol is also being developed. As riluzole is however not used to treat NPC, exclusively the arimoclomol-only groups of these studies were assessed. In study 1311-001, the applicant investigated the repeated dose toxicity of arimoclomol for 13 weeks in male and female Sprague Dawley rats (n = 15 per sex and dose group) at 1800 and 2600 mg/kg bw/day at a q.d. dosing schedule. In study 1311-004, the repeated dose toxicity of arimoclomol was similarly assessed when administered for 13 weeks to male and female Sprague-Dawley rats, also at 1800 and 2600 mg/kg bw/day at a q.d. dosing regimen. In the latter study, also recovery groups were integrated.

The toxicity findings of the arimoclomol-only animals in these two studies are very similar to the ones already described in rat repeated dose toxicity studies. However, a remarkable finding was observed in study 1311-001: Ophthalmoscopic examinations revealed bilaterally increased density of the lens nucleus which appeared to be related to arimoclomol at dose levels of arimoclomol citrate at 1800 mg/kg/day and above, i.e. at dose levels exceeding the maximum tolerated dose and corresponding to at least 9-fold the human exposure. There was an arimoclomol-related increase in the ophthalmoscopic incidence of increased density of the lens nucleus in both eyes of 10 investigated males (100%) and 11 females (91.6%) dosed 1800 mg/kg/day. The applicant concluded that the toxicological significance of this finding is uncertain, and will include further ophthalmologic investigations in the to-be-submitted 2-year rat carcinogenicity study (submission is planned in August 2022 as a post-authorisation measure). However, given the high incidence of this unusual finding, a concern was originally raised on this aspect (further below).

3.2.5. Ecotoxicity/environmental risk assessment

The PEC surfacewater value of arimoclomol is below the action limit of 0.01 µg/L. Furthermore, the ion-corrected log D_{OW} (which is equivalent to the log K_{ow}) of arimoclomol is negative (Study 07418-004-001); therefore, arimoclomol is not expected to be a PBT substance.

3.2.6. Discussion on non-clinical aspects

Pharmacology:

The non-clinical primary pharmacology programme combines *in vitro* assessment in NPC patient derived fibroblasts, heterologous cellular systems and a murine $NPC^{-/-}$ animal model. Fibroblasts from skin biopsies of NPC1 patients and NPC1-/- mice represent appropriate preclinical *in vitro* and *in vivo* systems to establish primary pharmacology relevant in Niemann-Pick disease type C.

The exact target mechanism for arimoclomol is unknown. However, *in vitro* application of up to 400 µM arimoclomol significantly increased HSF1, HSP70 and the NPC1 cholesterol transporter. In response to a clock stop the applicant provided additionally four *in vitro* studies which highlight and expand the number of arimoclomol (400 µM) regulated genes (CLEAR genes), but failed to show significant effects below 400µM therein. At lower concentrations (<100 µM) arimoclomol improved morphology and cholesterol content of lysosomes in NPC patient derived fibroblasts. In this context it is difficult to understand how lysosomal lipid content improved without significant effects on increased expression of the NPC1 transporter at this low arimoclomol concentrations. Additional and alternative target of arimoclomol may exist and explain these heterogenic effects. Moreover, in secondary pharmacology arimoclomol was used to compete with radioligands at 10 µM in ligand binding assays. Summing up all

these *in vitro* results the specific molecular target of arimoclomol is currently unknown, but genes aetiologically linked to the pathomechanisms of Niemann-Pick disease are regulated by arimoclomol. The applicant proposed an adopted text for the SmPC section 5.1 (mechanism of action) which is deemed acceptable.

Unfortunately, hallmarks of cell injury in lysosomal storage disorders like autophagy and viability were not investigated. Similarly, a robust determination of EC_{50} values for arimoclomol effects is not submitted. Taken together, a concentration of 400 µM arimoclomol is considered to significantly enhance the heat shock response, CLEAR gene response and maturation of glycosylated NPC1 proteins in NPC patient derived fibroblasts.

Three abundant arimoclomol metabolites were identified in humans at steady state (M2, M5 and M105) and were pharmacologically ineffective with respect to the induction of HSP70 and enhancement of NPC1 protein levels in fibroblast cells from NPC1 patients.

Arimoclomol was also investigated *in vivo*, in an $NPC1^{-/-}$ mouse model. The animal model mimics the motoric and morphological impairments of NPC disease and is therefore considered suitable to evaluate efficacy of arimoclomol. Arimoclomol was orally applied in daily doses of 1-300 mg/kg (Kirkegaard et al. 2016; study no. CRO-1211210031). While data within the publication Kirkegaard et al. are consistent, this is not the case if including the data from study no. CRO-1211210031 (Kirkegaard et al. 2016). These discrepancies were attributable to the source of the *Npc1-/- mice* (CRO/QPS or University of Oxford), which elicited differences in behaviour and disease phenotype as stated by the applicant.

Arimocolomol (10 mg/kg orally) significantly activates HSF1 and augments HSP70 protein levels in brains, but not in liver tissue of $NPC1^{-/-}$ mice. The applicant explains thise observation by tissue specific expression and nuclear turnover of HSF1, which is less responsive to arimoclomol in the liver. Gait parameters also improved under arimocolomol (10 mg/kg orally) treatment. However, a stringent dose-dependency of arimoclomol induced effects is not provided. There is no ED_{50} calculated or provided so that one cannot estimate a safe and effective dose in $NPC1^{-/-}$ mice. Most of the arimoclomol data provided by Kirkegaard et al. were generated with 10 mg/kg orally (Kirkegaard et al. 2016). In contrast, gait analyses in study no. CRO-1211210031 was set up to 300 mg/kg arimoclomol and again no clear dose-response correlation (or ED50) is provided in this study (study no. CRO-1211210031). Thus, discrepancies in efficacy between the motoric analyses between Kirkegaard et al. 2016 and study no. CRO-1211210031 may be attributable to using *Npc1-/-* mice of different souces (CRO(QPS) versus University of Oxford). Since the applicant has not identified the source of the differences in the onset and extent of gait disturbances and motor deficits in these to animal studies, it is difficult to understand a causal dose-effect relationship for arimoclomol *in vivo*.

These data are somehow further supported by the new draft study report (CRO-1707310132) in the Npc1-/- mouse model, investigating the survival and behaviour in presence of arimoclomol and miglustat combinations. While median survival days of controls increased under arimoclomol from 84.5 days to 90 days, miglustat significantly expanded the survival to 120 days compared to arimoclomol. The combination of arimoclomol plus miglustat significantly extended the median lifespan to 143 days and thereby was more effective than arimoclomol alone. Importantly, the combination of arimoclomol plus miglustat compared to miglustat alone had no additional effect on behaviour of motor function at any time point or functional test. Thus, the mechanism(s) behind expanded survival with the combination of arimoclomol plus miglustat is therefore not linked to behaviour and improved motor function.

The evaluation of the arimoclomol potency and efficacy from the preclinical data is difficult, in particular due to the fact that an unclear mechanism of action with possibly multiple targets is proposed.

Hence, the applicant has stated the current level of uncertainty with respect to an unclear mechanism of action for arimoclomol in the SmPC.

The core battery studies on secondary pharmacology, assessing the cardiovascular and central nervous system (CNS) effects as well as respiratory function were conducted in accordance with the ICH S7 guidelines and good laboratory practice (GLP). Effects on the cardiovascular system were assessed in cell culture as well as in rats and dogs. Some cardiovascular endpoints were incorporated in repeat-dose general toxicity studies in dogs (GLP). The lowest concentrations (7 µM) of arimoclomol metabolites, M2 and M105 inhibited hERG currents by 21.0% and 27.8%, respectively. Moreover, M2 and M105 mediated effects on hERG activity were not or only partially reversed after the washout period. Further, the QTc intervals were assessed in several repeat-dose toxicity studies in dogs and revealed a 10% QTc prolongation with arimoclomol. Considering arimoclomol as a long-term therapy hERG inhibition and slight QTc prolongation are deemed to exert arrhythmic potential, which is considered of special concern as stated below.

With respect to drug-drug interactions, arimoclomol prolonged the pentobarbital sleeping time in rats and accelerated the hypnotic onset. The applicant stated that no noteworthy effects were observed on binding of the radioligands specific for the benzodiazepine binding site of $GABA_A$ receptors. Since epileptic seizures are common in NPC disease especially in paediatric patients, benzodiazepines and anti-convulsants are more often prescribed. Accordingly, *in vitro* no pharmacodynamic interaction with benzodiazepines was observed with arimoclomol (10 µM). Similarly, no noteworthy interaction with calcium- and sodium-channels, glutamate- and $GABA_A$ receptors have been observed in the secondary pharmacology screen so that a drug-drug interactions with anti-convulsant medication and arimoclomol is unlikely.

A concern in the quality section expressed that further information is needed on the potential differences in the biological activity of the E- and Z-isomers of the drug substance and their relative proportions in the non-clinical and clinical batches. Arimoclomol is highly stable as confirmed by a recent study using reverse phase LC-MS of rat plasma, human plasma or urine samples (Study Number 8473272). Further, the configuration of arimoclomol is considered stable when stored as demonstrated by the ongoing accelerated and long-term stability studies, since no increase in the amount of S-enantiomer, and no detection of the E-isomer have been seen within 24 months. The conversion of Z- to E-isomers in plasma is highly unlikely due to a considerable steric hindrance. Nevertheless, exposure to 1.2 million lux hours as per ICH Q1B, indicated that the conversion from Z-isomer to E-isomer is limited. Further, the E-isomer was not found in any of the analysed rat plasma, human plasma or urine samples, so that one may consider no isomerisation in plasma between E/Z-isomers. In conclusion, arimoclomol is a highly stable compound, so that it is justified to omit investigation of the biological activity of the E-isomer and S-enantiomer.

Pharmacokinetics:

After the D80 assessment, seven other concerns on non-clinical pharmacokinetics were identified. However, the applicant succeeded in resolving all these concerns.

AUC and C_{max} levels of arimoclomol were frequently lower after chronic dosing than after single dose administration (e.g. in toxicokinetic evaluations). At some points of the dossier this effect was explained by the potential induction of arimoclomol-metabolising enzymes. However, it was not discussed which metabolising enzymes could be responsible in this respect. In the D120 responses, the applicant clarified that this pharmacokinetic peculiarity was indeed only observed in rodents, and that no similar trend was observed in larger laboratory animals (rabbits and dogs) and in humans. Therefore, the applicant concluded that this observation in rodents is most likely not relevant for humans.

As arimoclomol is ionised at the physiologically relevant pH (pH 5 –9), its claimed Log K_{OW} is negative. Therefore, arimoclomol can be considered lipophobic. Nevertheless, arimoclomol is rapidly absorbed upon oral administration (in animals and in humans), and must cross cell membranes to unfold its pharmacologic mode of action. The applicant did originally not discuss how the rapid cell membrane crossing of arimoclomol can be explained despite its negative Log K_{OW}. The applicant responded that for drugs, not only the lipophilicity is relevant to understand cell membrane crossing, but also other endpoints which are summarised in Lipinsky's rule of five (number of hydrogen donors, hydrogen acceptors, molecular weight and Log P). The applicant further described that these endpoints predict that arimoclomol will efficiently cross cell membranes. In addition to this claim, the applicant submitted an additional validated Caco-2 study in the day 120 submission (Study 7027-121) which demonstrated rapid cell-membrane crossing. Considering all these aspects, the concern was considered resolved.

It was noted that the decrease kinetics of arimoclomol-related radioactivity was considerably slower in eyes than in pigmented skin of LE rats (e.g. after 1 and 240 hours, radioactivity was 88.9 and 1.49 µg equivalents ^{14}C-BRX-345 per gram pigmented skin, whereas radioactivity was still 165 and 72.0 µg equivalents ^{14}C-BRX-345 per gram eyes, respectively). The applicant was expected to explain this striking difference in elimination kinetics of arimoclomol related radioactivity between both melanin-containing organs. In the D120 responses, the applicant speculated that melanin-binding radioactivity was lost in study 7027-121 due to the shaving of the skin prior liquid scintillation counting. This is considered plausible. However, it is not clear whether loss of radioactivity via skin shaving and the subsequent loss of hair might indeed account for the striking differences in radioactivity observed between the eyes and the skin. Therefore, it should be concluded from study 7027-121 that the eyes are most probably a more potent sink for arimoclomol (and arimoclomol related material) than the skin.

The potential to induce pharmacokinetic drug interactions was only assessed for the arimoclomol-metabolite M2, but not for the two other important arimoclomol metabolites M105 and M5 (all three metabolites were found to be above 10% in human plasma). Such assessments could potentially be clinically relevant as non-clinical studies demonstrated that the elimination kinetics of arimoclomol metabolites can be considerably slower than of their parent substance, which leads to higher steady-state exposure during chronic treatment. Hence, a concern was originally raised on this issue. However, the applicant clarified in the D120 responses that M5 and M105 are not expected to pose a risk for clinically relevant drug interactions.

<u>Toxicology:</u>

In the D80 assessment, one major objection and 17 other toxicological concerns were originally identified. With the D120 responses, the applicant succeeded to resolve most of these concerns. However, for some aspects, outstanding concerns were subsequently raised. These outstanding concerns were ultimately resolved with the applicant's responses to the D180 LoQ.

It was originally doubted that the submitted genotoxicity studies sufficiently assessed the potential mutagenicity of the metabolites of arimoclomol at time of MAA. As to this deficiency, a major objection was originally raised in the D120 list of questions. In the D120 responses, the applicant provided GLP-compliant Ames tests for M2 and M105 (Study No. 8468128 and Study No. 8468125, respectively) that demonstrated that both metabolites were negative in the bacterial reverse mutation assay. Therefore, this major objection was considered resolved. Of note, the finalised reports of these studies were submitted in the responses to the D180 LoQ.

In patients, arimoclomol will likely be administered in combination with miglustat. Yet, no information on combinatory toxicology of concomitantly administered arimoclomol and miglustat was available at MAA. Hence, the applicant was originally expected to thoroughly discuss whether combinatory toxicology can be expected when treating patients with both pharmaceuticals. In the D120 responses,

the applicant acknowledges that some of the same target organs/tissues were identified in the toxicity studies with miglustat and arimoclomol, and that additive effects cannot be completely excluded. However, the applicant concluded that combinatory toxicity studies are not warranted, especially because of the 3R principle and the already gathered clinical data. This is understood and supported.

The applicant did – at the beginning of the MAA – not discuss how arimoclomol induces the heat shock response. It is conceivable that arimoclomol stimulates the heatshock-response by altering "healthy" proteins. Some toxicological observations indeed indicate that arimoclomol interacts with, and potentially denaturates, proteins. For example, high incidences of increased lens densities were observed in the rat study 1311-001. Similar ocular observations were also found in clinical studies. Furthermore, arimoclomol was classified as moderate skin sensitiser in study 00/544-104T, indicating that it is antigenic, likely through a hapten-mediated mechanism. Both these effects can be explained by protein denaturation induced by arimoclomol.

Considering this, the applicant was expected in the D120 list of question to thoroughly discuss whether arimoclomol-induced alteration of proteins could be (partly) responsible for the following toxicities observed in the submitted non-clinical studies:

- increased lens densities and subsequently cataracts;

- pre- and post-implantational embryonic as well as foetal toxicity;

- skin sensitisation and potentially antigenicity;

- clinical signs related to central nervous system impairments;

- local toxicity of highly exposed tissues, such as the observed severe irritation of the gastrointestinal mucosa at high arimoclomol doses;

- toxicity to rapidly proliferating cells, such as the observed adverse effects to haematopoietic cells (erythrocytes and leucocytes), gastrointestinal epithelial cells and cells of the reproductive tract (spermatocytes and ovary cells).

The applicant provided a thorough answer to this concern. However, the applicant could not exclude a pathogenic contribution of arimoclomol-related protein denaturation to many of the observed toxicities in non-clinical studies (lens alterations, skin sensitisation possibly by hapten-mediated antigenicity, pre- and post-implantational embryonic and foetal developmental toxicity as well as toxicity to male and female fertility, central nervous system impairments, gastrointestinal mucosal irritation, adverse effects to haematopoiesis). Similarly, the applicant could not exclude that protein denaturation by arimoclomol constitutes its pharmacologic mode of action (as heat shock response inducer). Therefore, it is well conceivable that protein denaturation by arimoclomol causes its pharmacologic mode of action (heat shock response induction), but also could induce many of the toxicities observed in non-clinical studies.

Throughout the submitted single dose toxicity (LD_{50}) studies, the applicant stated that the cause of the observed mortalities in mice and rats was circulatory insufficiency. Note that after intravenous administration of a lethal dose, the animals died within seconds to a few minutes. No detailed information on the pathogenesis of the arimoclomol-related circulatory failures was provided. Therefore, the applicant was originally expected to better explain the causes of the lethal circulatory insufficiencies in rodents after administration of a lethal arimoclomol dose. Furthermore, the applicant was originally expected to discuss whether similar lethal effects can be expected in patients ingesting a high overdose of arimoclomol (e.g. suicide attempts), and at which overdose such serious or even lethal circulatory effects could become apparent.

In response to this concern, the applicant acknowledges that it is possible that an overdose of arimoclomol could also lead to serious effects and/or lethality in humans. Specifically, the applicant concludes that it cannot be excluded that an intentional overdose (e.g. suicide attempt) with a dose several fold above the therapeutic dose may cause severe clinical effects and mortality. Therefore, the applicant was expected to mention the single dose toxicity studies including the LD50 values and especially the rapid cardiac insufficiencies after administration of a lethal dose in section 5.3 of the SmPC. Furthermore, the Applicant was expected to mention in section 4.9 of the SmPC that – based on non-clinical single dose toxicity studies – it cannot be excluded that a high overdose of arimoclomol could rapidly lead to serious effects and/or lethality in humans. These demands were adequately incorporated in the SmPC.

In the D120 list of questions, multiple concerns were raised on non-clinical cardiovascular aspects:

The Applicant was expected to provide a thorough discussions on the following observed ECG and cardiac alterations in arimoclomol-exposed dogs, their pathogenesis in relation to arimoclomol administration, their toxicological relevance, and their relevance for the clinical use of arimoclomol:

- Decreased P wave amplitudes in test article groups in the chronic dog toxicity studies 00/544-107K and 05/982-201K;

- Increased QRS complex amplitudes and QRS prolongation in study 05/982-201K;

- Decreased heart weights in test article groups of study 00/544-107K.

Regarding the latter, the applicant was further expected to discuss why heart weights were not examined in the pivotal dog repeated dog toxicity study 05/982-201K.

In the applicant's D120 response to these concerns, a relation of the observed P wave alterations in dogs to arimoclomol administration could not be excluded. Similarly, a relation of prolonged QRS intervals in dogs to arimoclomol administration could not be entirely excluded. However, the applicant speculates that these ECG alterations are of no toxicological relevance, and points out that no similar P wave alterations and QRS interval prolongations were found in the thorough QT clinical trial (Study OR-ARI-TQT-01). Therefore, this concern was considered resolved.

Embryo-foetal toxicity of arimoclomol appeared more extensive when particular doses were administered at a thrice a day (t.i.d.) schedule compared to a once a day (q.d.) one. The two submitted juvenile toxicity studies, the FEED (fertility and early embryonic development) study and the PPND study were conducted with a q.d. dosing regimen, whereas the clinical arimoclomol administration is based on t.i.d. administration. As the dosing schedule was not representative for the clinical use of arimoclomol, the applicant was invited to discuss whether t.i.d. dosing in animals can – analogously as observed in EFD studies – be expected to result in more extensive juvenile, FEED and PPND toxicity than the one observed in the submitted studies in which a q.d. dosing regimen was used. The applicant clarified that a q.d. dosing regimen would not have been possible in the juvenile toxicity study. Furthermore, in regard to the FEED study, the applicant clarified that adverse effects were already described and also mentioned in the SmPC. As the conduct of FEED and PPND studies with a q.d. dosing regimen is not considered relevant for conducting proper risk mitigation (because the respective data from studies employing a t.i.d. schedule are already available), and as the conduct of new studies would therefore contradict the 3R principles, the applicant does not consider new studies warranted. Even though it should be noted that the conducted FEED and PPND studies do not sufficiently represent the clinical dosing regimen, the applicant's position is understood and acknowledged.

In study 00/544-104T, arimoclomol was classified as moderate skin sensitiser. The applicant did not provide a discussion on these results. However, based on the moderate skin sensitising potential, it

can be presumed that arimoclomol possesses antigenic capacity, most likely via a hapten-mediated mechanism. The applicant was therefore expected to discuss whether arimoclomol could induce hapten-mediated antigenicity. Furthermore, the applicant was expected to broadly discuss the safety implications of hapten-mediated antigenicity of arimoclomol, with a special focus on gastrointestinal sensitisation and subsequent irritation. In the responses to this concern, the applicant could not exclude the possibility of hapten-mediated antigenicity of arimoclomol.

Arimoclomol absorbs UVB with wavelengths around 300 nm. Furthermore, it has a molar extinction coefficient in the range of natural sunlight (290-700nm) of 3602 L/mol.cm, therefore it can be expected to be sufficiently photoreactive (ICH S10). The rat biodistribution study 7027-121 demonstrated that arimoclomol considerably accumulates in eyes (e.g. at 240 hours post-dose, the high levels of arimoclomol-related material in the eyes represented an eye:plasma ratio of 261!) and skin of pigmented long even rats (5 times higher compared to the non-pigmented skin of rats in study 0018).

Approximately 2% of UVB light at 300 nm reaches the eye lenses (Lucas RM 2011, doi: 10.1097/ICL.0b013e31821cb0cf). It was therefore considered well conceivable that the observed ocular toxicity of arimoclomol in particular rat studies and to a certain extent in clinical studies could be (partly) related to a phototoxic activation of arimoclomol in the eyes. In addition, UVB is mainly absorbed in the epidermis; some UVB may reach the dermis (D'Orazio et al, 2013; DOI: 10.3390/ijms140612222).

As there are limited data from clinical trials on adverse events, justification based on clinical trials data is not sufficient for photosafety assessment of the substance and additional data (e.g., *in vitro* phototoxicity assay results) should be provided. Because of these concerns, the applicant submitted an *in vitro* 3T3 Neutral Red Uptake phototoxicity assay with arimoclomol in the D180 responses (Study 20315652). In this study, arimoclomol was ultimately classified to be non-phototoxic. This interpretation is supported, and the concerns on phototoxicity were consequently resolved.

In study 1311-001, there was an arimoclomol-related increase in the ophthalmoscopic incidence of increased density of the lens nucleus in both eyes of 10 investigated males (100%) and 11 females (91.6%) dosed 1800 mg/kg/day. A relation of this finding to arimoclomol administration seems likely as almost all arimoclomol-administered animals were affected. It is not clear why such ocular alterations were particularly observed in study 1311-001 and not in other repeated dose toxicity studies. The applicant was originally invited to thoroughly discuss this issue, to propose a pathomechanism that could explain this finding, and to discuss the toxicological significance of this finding. The Applican responded to this concern that the lens changes observed in the rat study No. 1311-001 could be related to the accumulation of arimoclomol-related material in the eyes. Furthermore, the applicant could not exclude the hypothesis that the observed lens alterations in non-clinical (and potentially clinical) studies were related to the arimoclomol-related denaturation of lens proteins.

<u>Environmental risk assessment:</u>

In total, one concern was identified on the applicant's environmental risk assessment: The applicant was asked to provide an experimental logK_{OW} value including a full study report in accordance with EMA/CHMP/SWP/44609/2010 Rev. 1, Question 6. The applicant submitted Study 07418-004-001; the concern is therefore considered resolved.

3.2.7. Conclusion on non-clinical aspects

The applicant succeeded in resolving all concerns raised throughout the marketing authorisation application procedure. Consequently, marketing of arimoclomol (Miplyffa) is supported by the submitted non-clinical studies.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Figure 1-2 Arimoclomol Clinical Development Programme

Clinical Pharmacology Trials

Completed Single Dose trials
Single-ascending Dose (CLT P1-001)
40338
Absorption, metabolism, and excretion
AALS-002
Bioavailability and food interaction
AALS-004
AALS-011
Hepatic impairment
(ongoing at safety data cut 31 July 2020)
OR-ARI-HEP-01*

Completed Multiple Dose trials
Multiple-ascending Dose (CLT P1-002)
40343**
AALS-005**
Renal safety
AALS-010
Multiple-dose PK of arimoclomol and its metabolites
OR-ARI-MET-01

Ongoing
Renal impairment
OR-ARI-REN-01
QT/QTc interval prolongation
OR-ARI-TQT-01

* Ongoing at the safety data cut-off, 31 July 2020. The clinical trial report was completed before this submission.
** Some multiple dose trials include an initial SD dose

Clinical Trials

Trials in NPC

Completed
Observational, disease progression (natural history)
CT-ORZY-NPC-001
Double-blind, randomised, placebo-controlled followed by:
- open-label extension (ongoing)
- sub-study in patients below 2 years (ongoing)

CT-ORZY-NPC-002

Trials in Other Indications

ALS
Completed
Double-blind, randomised, placebo-controlled (PK and Cerebrospinal fluid penetration)
AALS-001
Open-label extension of AALS-001
AALS-001OL
Investigator-initiated, double-blind, randomised, placebo-controlled (20100758)
ALS SOD1
Ongoing
Double-blind, randomised, placebo-controlled
ORARIALS-01
Open-label extension of ORARIALS-01
ORARIALS-02

IBM
Completed
Investigator-initiated, double-blind, randomised, placebo-controlled
10656
Ongoing
Double-blind, randomised, placebo-controlled
IBM4809
Open-label extension of IBM4809
IBM-OLE

GD
Ongoing
Double-blind, randomised, placebo-controlled followed by open-label extension
ORARIGAU-01

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Table 1-1 Overview of Clinical Pharmacology Trial

Trial	Trial Type/Trial Design	Treatment Duration	Dose	Subjects/Patients (n)	
				Placebo	Arimoclomol
40338 (BRX-345 CLT P1-001)	A single-ascending dose trial to investigate safety, tolerability and pharmacokinetics of arimoclomol in healthy men	Single dose	31, 62, 124, 248, 372 and 496 mg	2[a]	10[a]

Trial	Trial Type/Trial Design	Treatment Duration	Dose	Subjects/Patients (n)	
				Placebo	Arimoclomol
AALS-005	A randomized, double-blind, placebo-controlled single- and multiple dose escalation trial to investigate safety, tolerability and pharmacokinetics of arimoclomol in healthy men	Day 1 single dose, Days 2-5 multiple t.i.d. doses, Day 6 single dose	62 mg t.i.d. (186 mg/day), 124 mg t.i.d. (372 mg/day), 248 mg t.i.d. (744 mg/day), 372 mg t.i.d. (1116 mg/day)	12	28
OR-ARI-MET-01	An open-label, multiple-dose trial to investigate pharmacokinetics of arimoclomol and its most abundant metabolites in healthy men	Days 1-5 multiple t.i.d. doses, Day 6 single-dose	248 mg t.i.d.	0	6
AALS-001	A randomized, double-blind, placebo-controlled trial to investigate the safety and tolerability following 4 weeks administration of arimoclomol to patients with ALS.	Multiple t.i.d. doses for 28 days	16 mg t.i.d. (47 mg/day), 31 mg t.i.d. (93 mg/day), 62 mg t.i.d. (186 mg/day)	11	33
AALS-002[b]	An open-label trial investigating the absorption, metabolism, and excretion (AME) of arimoclomol following a single oral dose of 14C arimoclomol to healthy men.	Single dose	62 mg (3.7 MBq; 100µCi)	0	6
AALS-004[c]	Open-label, single-oral-dose, two-way crossover, food-effect in healthy subjects	2 single doses	62 mg	0	18
AALS-010[a]	28-day randomized, placebo-controlled, multiple-dose trial investigating the effect of arimoclomol on glomerular function, renal haemodynamics and tubular function in healthy men	Multiple t.i.d. doses	248 mg t.i.d. (744 mg/day)	4	12
AALS-011	Open-label, single-oral-dose, two-way crossover, food-effect in healthy subjects	2 single doses	248 mg	0	20
OR-ARI-HEP-01	An open-label, single-dose trial investigating the pharmacokinetics of arimoclomol in subject with	Single dose	248 mg	0	24

The clinical pharmacology assessment included in the application was based on several clinical studies examining single-dose and multiple-dose PK, bioequivalence of clinical-trial and market-image formulations, relative bioavailability, mass balance/absorption, distribution, metabolism, and excretion

(ADME), food effect, drug interactions as well as impact of hepatic impairment. In addition, a population PK model was used to estimate population PK parameters as well as to characterise exposure-response relationships.

The pharmacokinetic data from the individual clinical pharmacology studies with arimoclomol have been summarised by non-compartmental pharmacokinetic analysis of data from 6 clinical pharmacology studies including 112 healthy subjects to provide overall descriptive statistics of the pharmacokinetic parameters of arimoclomol. Population PK analysis utilised pooled PK data collected from 6 studies and included a total of 134 subjects with 2571 concentration records. Overall, the observed plasma concentrations were in agreement with simulated data.

The selected population covariate PK model was used to simulate exposure variables $AUC_{0\text{-}8h,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for the 34 subjects in CT-ORZY-NPC-002 who contributed to the exposure-response analysis. Analysis of exposure variables and covariates for their influence on the slope parameter revealed that co-administration of miglustat was associated with a sizeable decrease in the slope. The association was statistically highly significant and accounted for 92% of the variance of the inter-individual variability in the slope. However, considering the low observed IIV in the group with co-administrated miglustat and rapporteur considerations about efficacy in patients with co-administration of miglustat and those without, the issue is not further pursued.

Bioanalytical methods

Arimoclomol was initially quantified using a HPLC-UV method, but more recently different LC-MS/MS methods have been developed and validated for quantification of Arimoclomol and metabolites M2, M5 and M105 in different matrix. Several labs were used: Toxicological Research Centre (TRC); MicroConstants Inc.; Covance Laboratories and PRA Health Sciences. First bioanalytical methods for the determination of Arimoclomol in human serum samples were developed approximately 20 years ago during the development course of Miplyffa. It should be noted that the methods evolved in accordance with the requests from the former FDA Guidance for Industry (2001) and its subsequent updates, and later the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) was also followed and any deficiency was assessed in the context of time. Validation reports are included in the dossier. Most of the validation reports contain statements that validations were performed following GLP principles.

The inter- and intra-assay precision and accuracy for all assays of Arimoclomol and its metabolites in human plasma, serum, urine and CFS samples were within the acceptance criteria for the chosen QC samples. Although ISR analysis have been applied only for those studies conducted after the recommendation came into a force (Trial OR-ARI-MET-01 and Trial OR-ARI-hep-01), the results were within the acceptance criteria recommended by EMA guideline (±20%) and therefore bioanalytical results can be considered reliable and reproducible

- **Absorption**

Arimoclomol is readily absorbed after oral administration of capsules. Following multiple doses of 62 to 372 mg (186 to 1116 mg/day), median tmax values of 0.25 to 3 hours were observed, and in the human AME trial, 77.5% of the radiolabelled dose was recovered in the urine and 12.0% in faeces indicating relatively quick and extensive absorption following oral administration.

The popPK model has estimated Ka value around 0.338 h with CV= 48.5%, the age was suggested as important factor for absorption.

Bioavailability

The absolute bioavailability of arimoclomol in humans was not investigated.

In rats the absolute bioavailability of arimoclomol following oral administration was 84% and 75 % in dogs relative to arimoclomol i.v. administration (based on AUC0-inf).

Bioequivalence

A BCS-based biowaivers is requested to establish bioequivalence between early clinical trial products and to-be-marketed products.

For the blinded phase of the clinical Phase 2/3 trial, CT-ORZY-NPC-002, a capsule formulation with excess amount of excipient material for the lower capsule strengths was required in order to ensure blinding. The capsule formulation was then modified between the blinded and the open label (OL) phase of the CT-ORZY-NPC-002 trial in order to optimise it for the patients by reducing the capsule fill weight and the amount of excipients to be taken with each capsule. Furthermore, the gelatine capsule shell was replaced with a shell of hydroxypropyl methyl cellulose (HPMC).

To further ease compliance and avoid the ingestion of multiple capsules three times a day, a specific capsule strength for each recommended dose has since then been developed for the to-be-marketed product covering each of the 5 weight bands. Consequently, the quantitative composition of the excipients was modified slightly for some of the strengths between the OL phase of the CT-ORZY-NPC-002 trial and the to-be-marketed product.

The biowaiver of bioequivalence studies between the formulations used in the pivotal CTORZY- NPC-002 clinical trial (reference product) and the to-be-marketed drug products (test product) is requested based on the following elements:

a. Following oral administration of arimoclomol, absorption is both rapid and extensive. In the human absorption, metabolism, and excretion (AME) trial, 77.5% of drug-related material was recovered in the urine and 12% in faeces. Therefore, in conjunction with the data demonstrating high solubility under all physiological pH conditions, arimoclomol citrate can be characterised as a **BCS Class 1** drug substance.

b. Excipients across the different formulations are qualitatively the same and are known not to affect the rate and extent of drug absorption

c. An *in vitro* dissolution study comparing clinical trial products (reference product) and the to-be-marketed drug products (test product) demonstrate very rapid dissolution characteristics, i.e. ≥ 85% dissolved within 15 minutes, under the biowaiver guidance dissolution conditions at pH 1.2, 4.5 and 6.8. The dissolution profiles are thus considered similar without the need for comparison using an f2 test and of low risk for any formulation related impact on the resulting pharmacokinetics.

d. A Design of Experiment study has shown that changes to the formulation within the Proven Acceptable Ranges of the process parameters did not have any significant effect on the dissolution profiles which all remained within specifications and showed very rapid dissolution.

e. Arimoclomol is not intended for absorption in the oral cavity.

f. Bioequivalence between formulations is supported by comparable dose normalised exposure levels (maximum observed plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC0-inf)) across the different formulations used in the clinical trials conducted with arimoclomol during the clinical development programme.

g. Arimoclomol citrate is not considered a drug substance with a narrow therapeutic index

Dissolution study of P741 arimoclomol citrate capsules at 3 different pH conditions In support of biowaiver

Dissolution testing were carried out in an Apparatus 2 at 75 rpm using 900 mL of the following dissolution media:

- (1) Hydrochloric acid medium, pH 1.2;

- (2) Acetate buffer solution, pH 4.5;

- (3) Phosphate buffer solution, pH 6.8.

Twelve dosage units for each strength of the test and reference drug product were evaluated in two separate sequences of 6 capsules each. Samples were collected at the time-points 5, 10, 15, 20, 30, 45 and 60 minutes to characterise the full dissolution profile of the drug product.

- Batch 8211X (124 mg validation batch) – test product formula

- Batch 8602X (93 mg validation batch) – test product formula

- Batch 8106X (62 mg validation batch) – test product formula

- Batch 8502X (47 mg validation batch) – test product formula

- Batch 8404X (31 mg validation batch) – test product formula

- Batch 16E03C (31 mg CTM batch) – reference product formula

- Batch 16F07C (62 mg CTM batch) – reference product formula

Results

For the reference product, both the 31 mg and the 62 mg dosage strength clearly show very rapid dissolution characteristics.

For the test products, the 31 mg, 47 mg and 124 mg capsule strengths all dissolve in average 85% or more of the label claim of the drug within 15 minutes in all three dissolution media.

For the test product at 62 mg dosage strength, in average 85% or more of the label claim of the drug dissolves within 15 minutes at pH 1.2 and 4.5. However, at pH 6.8, in average 84% of the label claim is dissolved at 15 minutes.

Similarly, for the 93 mg dosage strength, where in average 85% or more of the label claim of the drug is dissolved within 15 minutes at pH 4.5 and 6.8, but at pH 1.2, in average 84% of the label claim is dissolved at 15 minutes.

An analytical investigation was performed on the results for the test product batches of 62 mg and 93 mg dosage strengths that failed to meet the criterion of ≥85% dissolved within 15 minutes at pH 6.8 and 1.2, respectively. Although no definitive methodological or analytical root cause could be established, it was found that these two tests showed the highest variability at 15 minutes in the whole study, RSD was 25.2 and 23.4% respectively. A Student's t-test showed a significant difference between the mean values obtained for sequence 1, i.e. vessel 1-6, and sequence 2, i.e. vessel 7-12 (Table 41).

Sample	Mean 1-6	Mean 7-12	RSD 1-6	RSD 7-12	p-value (t-test)	f2
8106X, pH 6.8	98.0	69.6	14.3	24.9	0.01086	32.4
8602X, pH 1.2	72.7	94.4	27.1	13.8	0.04846	36.8

Table 41: Comparison of test data obtained from vessel 1-6 vs. vessel 7-12

Individual differences in shell rupture and hydration of the capsule content leading to variability of dissolution between sequence 1 and 2 at early time points are considered the main contributors to the deviating results.

As the dissolution results in the pivotal stability study is obtained at the same pH 1.2 that showed a mean of 84% dissolved of the label claim at 15 minutes, the result for the 93 mg dosage strength in this study can be compared to the data of the pivotal stability study. The mean result in the stability study at 15 minutes is ≥90% at all 8 test points, indicating that the results obtained in this *in vitro* dissolution study are not representative of the test product. Corresponding stability data are not available for comparison of the 62 mg dosage strength at pH 6.8.

Influence of food

The effect of a high fat meal on the pharmacokinetics of 62 mg arimoclomol (Formulation D2) was determined in Trial AALS-004 and AALS-011.

No relevant effect of food on the pharmacokinetics of arimoclomol was observed.

- **Distribution**

Following multiple t.i.d doses of arimoclomol doses up to 372 mg (1116 mg/day), the estimated apparent volume of distribution (Vz/F) is approximately 230 L, which indicate extravascular distribution of arimoclomol.

Concentrations of arimoclomol-related material in serum and whole blood were generally similar, indicating that arimoclomol is not highly associated with red blood cells.

In vitro, binding of arimoclomol to serum proteins is low (approximately 10%). Binding appears to be independent of arimoclomol concentrations within the concentration range tested (125-5000 ng/mL).

Arimoclomol crosses the blood-brain-barrier as suggested by the dose-dependent increase in mean arimoclomol CSF concentrations in patients with ALS following 16, 31, or 62 mg t.i.d. dosing (47, 93, or 186 mg/day) for 28 days (Trial AALS-001).

- **Elimination**

Excretion

Arimoclomol is eliminated partly by urinary excretion of intact arimoclomol and partly by metabolism followed by excretion of metabolites in urine and faeces. In the single-dose AME trial with 14C-arimoclomol, 89.5% of the drug-related material was recovered over 312 hours with 77.5% recovered in urine and 12 % in faeces. Approximately 42% of the dose was excreted as intact arimoclomol in the urine (Trials AALS-002 and OR-ARI-MET-01).

The estimated apparent total clearance (CL/F) of arimoclomol was approximately 40-50 L/h and the half-live was approximately 4 hours following single- and multiple t.i.d doses of arimoclomol Table 3-1 and Table 3-2).

Additionally, based on the renal clearance value of arimoclomol reported in the OR-ARI-MET-01 trial (18.6 L/h, CV% 20), approximately 30% is due to active transporter processes (renal filtration rate = GFR ·fu = 7.2 L/h·0.9=6.5 L/h; 6.5 L/h/18.6 L/h = 0.3). *In vitro* studies indicated that transporters responsible for the active renal elimination of arimoclomol are MATE1 and MATE2-K.

In the popPK analysis, the overall population mean CL/F was estimated to be 39.9 L/h [popPK report], which is consistent with data based on the pooled non-compartmental pharmacokinetic.

The renal clearance (CLr) for arimoclomol was estimated to be 18.6 L/h (OR-ARI-MET-01) which is approximately 50% of total apparent clearance of 39.9 L/h [popPK report].

Metabolism

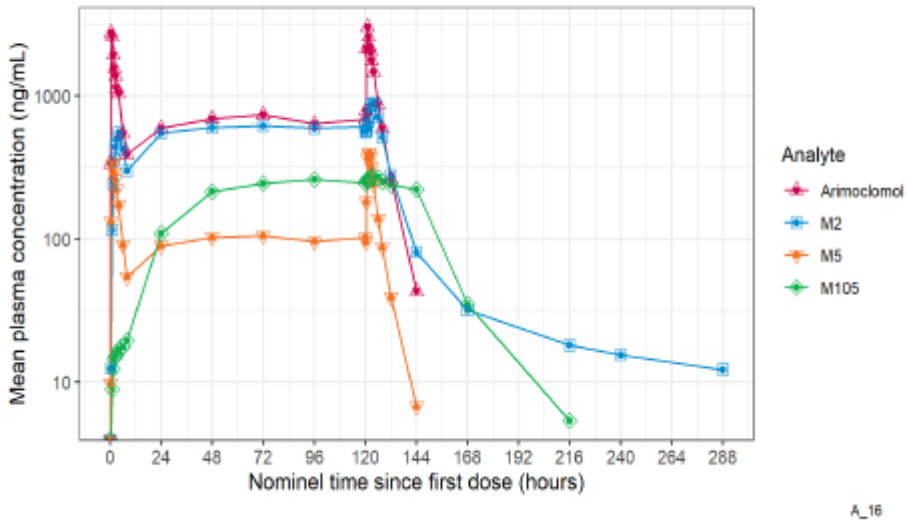
Metabolism of arimoclomol was investigated in the human AME trial which included metabolite profiling of plasma, urine and faeces (Trial AALS-002) and the 3 most abundant metabolites (M2, M5 and M105) were quantified in plasma and urine as part of the clinical trial (Trial OR-ARI-MET-01). In addition, several *in vitro* studies were conducted to identify the structure of the metabolites and the enzymes involved in the metabolism of arimoclomol (please see the non-clinical part for futher information).
In both clinical trials arimoclomol was the primary component in both plasma and urine. In AALS-002, arimoclomol accounted for 43% of the total amount of radioactivity circulating in plasma and approximately 42% of the dose was excreted as intact arimoclomol in the urine, which is in agreement with results from OR-ARI-MET-01 where 43% of the dose was excreted as arimoclomol in urine.
In vivo and *in vitro* studies together show that arimoclomol is metabolised by several routes and that the primary routes are by glutathionation, O-glucuronidation and NO-cleavage. The most abundant metabolites circulating in human plasma are the cysteine-conjugate (M2), the glucuronide (M5) and the cleavage product M105, which are also the most abundant metabolites in urine.

All *in vitro* and vivo metabolism studies formed indicate that metabolism of arimoclomol is similar between humans and nonclinical species. Results from metabolite profiling in plasma obtained from animals and humans document that all human circulating metabolites were present in higher amounts in the nonclinical species.

Pharmacokinetics of metabolites

The PK of arimoclomol and its metabolites was investigated in trial OR-ARI-MET-01 in six healthy young men aged ≥ 18 and ≤ 45 years. All subjects received 248 mg arimoclomol orally (capsules) t.i.d. (744 mg/day) on Day 1 to Day 5 and a single morning dose on Day 6. Plasma and serum samples were collected for up to 8 hours post-dose following the morning dose on Day 1, and plasma samples were collected pre-morning dose on Day 2, Day 3, Day 4, Day 5 , Day 6 and up to 168 hours post-dose following the last dose on Day 6. Urine was collected quantitatively up to 24 hours post-morning dose on Day 1, 2, and 6. The plasma exposure of arimoclomol and its metabolites M2, M5, and M105, following single- and multiple dosing, is illustrated in Figure 2-3 and the pharmacokinetic parameters are summarised in Table 2-5, below.

Figure 2-3 **Mean Plasma Concentrations of Arimoclomol and its Metabolites M2, M5, and M105 following Multiple-Doses of 248 mg t.i.d. – Trial OR-ARI-MET-01**



Source: [OR-ARI-MET-01, Listings 16.2.5.2 and 16.2.5.3].

Table 2-5 **Single- and Multiple-Dose Pharmacokinetic Parameters of Arimoclomol metabolites M2, M5 and M105 in Male Subjects – Trial OR-ARI-MET-01**

	248 mg SD Day 1 N=6			248 mg t.i.d. (744 mg/day) Day 6 N=6		
Parameter/ Analyte	M2	M5	M105	M2	M5	M105
$AUC_{0\text{-}8h}$ (h·ng/mL)	3774[a] (NA)	1275 (25)	135[a] (NA)	5632 (24)	1789 (18)	2010 (32)
$AUC_{0\text{-}inf}$ (h·ng/mL)	5892[a] (NA)	1462 (22)	NA[b]	-	-	-
C_{max} (ng/mL)	547 (17)	336 (34)	19.2 (28)	892 (22)	445 (25)	277 (32)
t_{max} (h)	4.0 (3.0,4.0)	1.3 (1.0,2.5)	8.0[d] (2.5,8.0)	3.5 (2.5,4.0)	1.5 (1.0,2.0)	6.0[d] (3.0,8.0)
$t_{½}$ (h)	4.2[a] (NA)	2.4 (14)	NA[b]	96.8 (9)	3.5 (17)	12.9 (12)[c]
AR	-	-	-	1.62[a] (NA)	1.4 (15)	16.1 (NA)[a]
MR (AUC)	0.42[e] (11)	0.15 (33)	0.04[e] (34)	0.61 (10)	0.16 (28)	0.50 (37)
MR (C_{max})	0.25 (43)	0.12 (49)	0.02 (32)	0.34 (24)	0.14 (36)	0.24 (37)

Geometric mean (geometric CV%) values are presented for all parameters except t_{max}. Median (min,max) values are presented for t_{max}. AR=Accumulation Ratio. MR=Metabolic Ratio based on either AUC or C_{max}. Example of MR formula MR (AUC) SD = (AUC_{inf} Metabolite/MW Metabolite) / (AUC_{inf} Parent/MW Parent). NA= Not Applicable

[a] not estimable in 5 subjects

[b] Not estimable in 6 subjects

[c] Not reportable in 1 subject due to the adjusted R^2 <0.7.

[d] 8 hours sample last sample in profile

[e] Based on $AUC_{0\text{-}last}$

Source: [OR-ARI-MET-01, Sections 11.4.5, 11.4.6, 11.4.7].

In addition, PK of arimoclomol and the metabolites M2 and M105 were investigated in a dedicated TQT trial (OR-ARI-TQT-01), including a total of 34 healthy male subjects. Metabolite M5 was not investigated in the trial, as it is an O-glucuronide and not of toxicological concern (ICH 2012). The trial was completed in December 2020 and was submitted to EMA together with the responses to the D120. The PK profiles of arimoclomol citrate, M2 and M105 were captured after single and multiple doses of arimoclomol. The maximum observed plasma concentration was 6900 ng/mL for arimoclomol citrate, 2270 ng/mL for M2 and 833 ng/mL for M105. After dosing, arimoclomol was rapidly absorbed with a median Tmax of 1 hour for both the therapeutic and supratherapeutic arimoclomol dose on Day 1 and Day 3. The mean arimoclomol citrate exposure over the dose interval of 8 hours (AUC0-8) increased from 5610 h*ng/mL after the therapeutic 124 (200) mg dose, to 18400 h*ng/mL after the supratherapeutic 372 (600) mg dose, both on Day 3. Therefore, a three-fold increase in dose level resulted in an at least 3 times higher mean exposure of arimoclomol citrate.

The mean terminal half-life (t1/2) of arimoclomol citrate in plasma on Day 3 was similar for the therapeutic and the supratherapeutic dose of arimoclomol (4.43 (11.6%) and 4.19 (9.7 %) hours, respectively). The metabolite M2 showed a slightly longer t1/2 (5.63 (10.4%) for the therapeutic dose and 5.40 (10.0%) for the supratherapeutic dose, as observed on Day 3) than arimoclomol citrate. As expected, the t1/2 for M105 could not be calculated as the terminal elimination phase for M105 plasma profile was not reached on Day 1 or Day 3 for neither the therapeutic nor the supratherapeutic arimoclomol dose. While the Day 1 plasma profiles showed rising M105 during the first dose interval of 8 hours, the Day 3 M105 profiles after t.i.d. dosing of both the therapeutic and supratherapeutic doses of arimoclomol show that M105 metabolite reached a steady state.

Table 11-2: Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Therapeutic Dose (200 mg) of Arimoclomol TID (Treatment A) on Days 1 and 3

Day	Parameter*	N	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C_{max}, ng/mL	34	299	64.7	193	291	448	21.6	292	21.4
	T_{max}, h$^{\Xi}$	34	--	--	2.50	4.00	6.00	--	--	--
	AUC_{0-8}, h*ng/mL	34	1520	343	892	1470	2360	22.5	1480	22.6
	AUC_{0-t}, h*ng/mL	34	1520	343	892	1470	2360	22.6	1480	22.6
	MR_{Cmax}	34	0.322	0.102	0.162	0.307	0.606	31.6	0.307	32.1
	MR_{AUC}	34	0.490	0.0736	0.325	0.470	0.655	15.0	0.484	14.9
3	C_{max}, ng/mL	34	535	144	315	509	947	27.0	517	26.9
	T_{max}, h$^{\Xi}$	34	--	--	2.50	3.50	5.00	--	--	--
	C_{min}, ng/mL	34	271	86.3	140	240	481	31.8	259	30.9
	AUC_{0-8}, h*ng/mL	34	3210	869	1880	3060	5690	27.1	3100	26.2
	AUC_{0-24}, h*ng/mL	34	5260	1620	2970	4740	10600	30.9	5050	28.7
	AUC_{0-t}, h*ng/mL	34	5260	1630	2970	4740	10600	30.9	5050	28.7
	ke, 1/h	34	0.124	0.0135	0.100	0.120	0.154	10.8	0.124	10.6
	$t_{1/2}$, h	34	5.63	0.587	4.50	5.76	6.93	10.4	5.60	10.6
	RacObs	34	2.13	0.431	1.48	2.06	3.94	20.3	2.09	17.9
	MR_{Cmax}	34	0.460	0.120	0.228	0.452	0.777	26.2	0.444	27.3
	MR_{AUC}	34	0.727	0.133	0.551	0.706	1.04	18.2	0.716	17.6

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s^2) - 1), where s^2 is the observed variance on the natural log-scale.
$^{\Xi}$: Median (min, max) reported for Tmax.
RacObs: Accumulation ratio was calculated as $AUC_{0-8, Day\ 3}/AUC_{0-8, Day\ 1}$.
*: For all subjects on Day 1, $t_{1/2}$, ke, and AUC_{0-inf} were not estimable due to undetermined ke or not reportable due to $\%AUC_{extrap}$ >20%.

Table 11-5: Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Supratherapeutic Dose (600) mg) of Arimoclomol TID (Treatment B) on Days 1 and 3

Day	Parameter*	N$^{\Delta}$	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C_{max}, ng/mL	34	993	199	650	983	1370	20.1	973	20.8
	T_{max}, h$^{\Xi}$	34	--	--	3.00	4.00	6.00	--	--	--
	AUC_{0-8}, h*ng/mL	34	5100	1060	3090	5050	7110	20.7	4990	21.7
	AUC_{0-t}, h*ng/mL	34	5090	1060	3090	5050	7110	20.7	4980	21.7
	MR_{Cmax}	34	0.326	0.0794	0.212	0.315	0.489	24.4	0.317	24.4
	MR_{AUC}	34	0.476	0.0763	0.363	0.462	0.662	16.0	0.471	15.5
3	C_{max}, ng/mL	34	1690	398	915	1680	2740	23.5	1650	24.1
	T_{max}, h$^{\Xi}$	34	--	--	0.52	4.00	5.00	--	--	--
	C_{min}, ng/mL	34	898	218	542	883	1460	24.3	873	24.3
	AUC_{0-8}, h*ng/mL	34	10200	2180	6260	10300	15100	21.4	9930	21.8
	AUC_{0-24}, h*ng/mL	34	16800	4100	10900	16700	27700	24.3	16400	23.8
	AUC_{0-t}, h*ng/mL	34	16800	4100	10900	16700	27700	24.3	16400	23.8
	ke, 1/h	33	0.130	0.0138	0.112	0.127	0.166	10.6	0.129	10.3
	$t_{1/2}$, h	33	5.40	0.539	4.18	5.46	6.19	10.0	5.37	10.3
	RacObs	34	2.01	0.238	1.38	2.01	2.45	11.9	1.99	12.5
	MR_{Cmax}	34	0.444	0.116	0.286	0.427	0.807	26.2	0.431	24.9
	MR_{AUC}	34	0.703	0.110	0.551	0.674	0.992	15.7	0.695	15.1

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s^2) - 1), where s^2 is the observed variance on the natural log-scale.
$^{\Xi}$: Median (min, max) reported for Tmax.
RacObs: Accumulation ratio was calculated as $AUC_{0-8, Day\ 3}/AUC_{0-8, Day\ 1}$.
*: For all subjects on Day 1, $t_{1/2}$, ke, and AUC_{0-inf} were not estimable due to undetermined ke or not reportable due to $\%AUC_{extrap}$ >20%.
$^{\Delta}$: $t_{1/2}$ and ke were not estimable for 1 subject on Day 3 due to undetermined ke.

Table 11-3: Summary Statistics of Plasma Pharmacokinetic Parameters of M105 Following the Therapeutic Dose (200 mg) of Arimoclomol TID (Treatment A) on Days 1 and 3

Day	Parameter††	NΨ	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C_{max}, ng/mL	29	12.4	6.16	5.41	11.1	37.6	49.6	11.4	41.8
	T_{max}, hΞ	29	--	--	2.50	7.83	8.05	--	--	--
	AUC_{0-8}, h*ng/mL	29	59.2	28.1	7.59	60.9	115	47.5	49.5	81.9
	AUC_{0-t}, h*ng/mL	29	59.2	28.1	7.59	60.9	115	47.5	49.5	82.0
	MR_{Cmax}	29	0.0308	0.0155	0.0112	0.0275	0.0687	50.4	0.0275	50.3
	MR_{AUC}	29	0.0451	0.0220	0.00425	0.0453	0.0939	48.8	0.0371	89.4
3	C_{max}, ng/mL	34	120	32.7	77.6	111	215	27.3	116	26.3
	T_{max}, hΞ	34	--	--	0.00	4.00	8.00	--	--	--
	C_{min}, ng/mL	34	92.0	27.6	47.9	84.9	167	30.0	88.2	30.0
	AUC_{0-8}, h*ng/mL	34	859	236	539	807	1540	27.5	830	26.6
	AUC_{0-24}, h*ng/mL	34	2570	737	1430	2490	4400	28.7	2470	28.0
	AUC_{0-t}, h*ng/mL	34	2570	739	1440	2490	4420	28.8	2470	28.0
	RacObs	29	25.7	33.2	6.68	13.0	142	129.0	17.0	93.6
	MR_{Cmax}	34	0.243	0.0946	0.0876	0.248	0.549	38.9	0.227	40.5
	MR_{AUC}	34	0.455	0.140	0.264	0.421	0.782	30.8	0.435	30.3

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s^2) - 1), where s^2 is the observed variance on the natural log-scale.
Ξ: Median (min, max) reported for Tmax.
RacObs: Accumulation ratio was calculated as $AUC_{0-8, Day\ 3}/AUC_{0-8, Day\ 1}$.
Ψ: PK parameters of M105 for 5 subjects were not estimable because the entire concentration-time profile was <LLOQ on Day 1
†† : $t_{1/2}$, ke, and AUC_{0-inf} for M105 could not be estimated for any profiles, as terminal phase was not reached on Days 1 and 3.

Table 11-6: Summary Statistics of Plasma Pharmacokinetic Parameters of M105 Followi the Supratherapeutic Dose (600) mg) of Arimoclomol TID (Treatment B) on Days 1 and 3

Day	Parameter††	N	AM	SD	Min	Median	Max	CV%	GM	GCV%
1	C_{max}, ng/mL	34	26.8	9.86	9.01	26.9	49.5	36.8	24.9	43.0
	T_{max}, hΞ	34	--	--	3.50	8.00	8.02	--	--	--
	AUC_{0-8}, h*ng/mL	34	131	63.6	20.9	135	280	48.6	113	67.9
	AUC_{0-t}, h*ng/mL	34	131	63.6	20.9	135	280	48.5	113	67.8
	MR_{Cmax}	34	0.0205	0.00918	0.00496	0.0187	0.0435	44.7	0.0184	53.1
	MR_{AUC}	34	0.0286	0.0147	0.00396	0.0270	0.0697	51.6	0.0241	72.9
3	C_{max}, ng/mL	34	389	120	208	359	800	30.9	373	30.1
	T_{max}, hΞ	34	--	--	0.00	3.50	8.00	--	--	--
	C_{min}, ng/mL	34	293	101	129	269	633	34.3	277	35.0
	AUC_{0-8}, h*ng/mL	34	2760	862	1340	2540	5600	31.2	2640	31.3
	AUC_{0-24}, h*ng/mL	34	8430	2550	4880	8100	18300	30.2	8110	27.8
	AUC_{0-t}, h*ng/mL	34	8440	2550	4880	8110	18300	30.2	8130	27.7
	RacObs	34	30.5	29.3	8.77	20.2	160	95.9	23.4	76.9
	MR_{Cmax}	34	0.246	0.126	0.0999	0.213	0.748	51.3	0.222	47.4
	MR_{AUC}	34	0.449	0.168	0.193	0.412	0.845	37.4	0.420	39.3

AM: Arithmetic Mean; SD: Standard Deviation; Min: Minimum; Max: Maximum; GM: Geometric Mean; CV%: Arithmetic CV which is equal to STD/AM*100; GCV%: Geometric CV which is equal to 100 x sqrt (exp (s^2) - 1), where s^2 is the observed variance on the natural log-scale.
Ξ: Median (min, max) reported for Tmax.
RacObs: Accumulation ratio was calculated as $AUC_{0-8, Day\ 3}/AUC_{0-8, Day\ 1}$.
†† : $t_{1/2}$, ke, and AUC_{0-inf} for M105 could not be estimated for any profiles, as terminal phase was not reached on Days 1 and 3.

- **Dose proportionality and time dependency**

Dose proportionality

Arimoclomol is considered dose proportional within the dose range 62 to 372 mg t.i.d. (186 to 1116 mg/day). To investigate the dose proportionality of arimoclomol following multiple doses, Cmax and AUC0-8 from all multiple-dose trials in healthy subjects were pooled.

Table 3-4 Dose Proportionality of Arimoclomol Following Multiple t.i.d. Administration – Pooled Data from Trials AALS-005, AALS-010, and OR-ARI-MET-01

Parameter (Units)	Dose Range	Slope	Slope (90% CI)
C_{max} (ng/mL)	62 to 372 t.i.d (186 to 1116 mg/day)	1.11	1.02 – 1.21
AUC_{0-8} (ng·h/mL)	62 to 372 t.i.d (186 to 1116 mg/day)	1.17	1.08 – 1.25

Source: Appendix, Table 6-3.
Dose proportionality assessments were performed by statistical analysis using a power model.

The population modelling did also confirm that pharmacokinetic of arimoclomol is linear within the dose range of 16 to 496 mg.

Time dependency

The CL/F was similar following single and multiple t.i.d. doses of arimoclomol (34 to 61 L/h; Table 3-3). From the popPK analysis, no apparent time-dependency or non-linearity was observed.

Table 3-3 Arimoclomol Oral Clearance Following Single Dosing and Multiple t.i.d. Oral Dosing of 31 to 372 mg – Trials 40338 (BRX-345 CLT P1-002), AALS-005, AALS-010, and OR-ARI-MET-01

Trial	Population	Dose mg t.i.d. (mg/day)	N	CL/F (L/h) SD (Day 1 of dosing)	CL/F (L/h) MD (Last day of dosing)
AALS-005	Men	62 (186)	7	60.6 (16)	52.0 (19)[a]
	Men	124 (372)	7	43.3 (20)	39.0 (22)[a]
	Men	248 (744)	7	53.8 (24)	45.4 (25)[a]
	Men	372 (1116)	7	43.4 (8)	37.7 (10)[a]
OR-ARI-MET-01	Young men	248 (744)	6	39.7 (17)	34.4 (18)[b]
AALS-010	Men	248 (744)	12*	43.2 (15)	37.4 (17)[c]

Source: Trials [40338, AALS-005, AALS-010, OR-ARI-MET-01]
Geometric mean (geometric CV%) values are presented.
*One subject withdrew on Day 11 and therefore was not included in the PK analysis for Day 28.
[a]Day 5
[b]Day 6
[c]Day 28

The accumulation index for arimoclomol (based on AUC0-8) was estimated to be 1.3 to 1.4 following multiple doses of 62 to 372 mg t.i.d (186 to 1116 mg/day). This is consistent with a mean half-life for arimoclomol of 3.0 to 4.4 hours and t.i.d. administration. No time dependency has been observed for the other pharmacokinetic parameters of arimoclomol.

PK in target population

Table 2-10 shows the summary statistics of arimoclomol exposure (AUC0-8h,ss, Cmin,ss and Cmax,ss) in CT-ORZY-NPC-002 for all patients and stratified by each of the 5 five weight bands.

Table 2-10 Summary statistics of arimoclomol exposure variables stratified by body weight band

Exposure variable	Statistic	8 to 15 kg	15 to 22 kg	22 to 38 kg	38 to 55 kg	>55 kg	All patients
	N	4	5	6	12	7	34
$AUC_{0\text{-}8h,ss}$ (h·ng/mL)	Minimum	1660.9	1800.1	1680.9	2143.6	2111.0	1660.9
	Maximum	2048.2	2529.9	3410.8	4815.3	5113.7	5113.7
	Median	1822.3	2099.3	2841.5	3129.4	3382.6	2841.5
	Arithmetic mean	1838.4	2115.3	2689.0	3153.6	3453.1	2825.9
	Arithmetic CV (%)	8.7	13.9	25.4	25.8	25.4	31.0
	Geometric mean	1833.2	2099.2	2608.8	3060.5	3358.6	2701.5
	Geometric CV (%)	8.7	13.8	28.3	25.9	26.1	31.1
$C_{max,ss}$ (ng/mL)	Minimum	303.8	315.6	290.7	372.7	378.1	290.7
	Maximum	386.7	425.2	645.8	840.0	1073.3	1073.3
	Median	338.4	364.8	513.1	630.5	744.9	513.1
	Arithmetic mean	341.8	371.1	497.0	608.0	734.5	548.3
	Arithmetic CV (%)	12.9	11.3	26.1	26.2	27.7	35.5
	Geometric mean	339.7	369.2	481.0	587.8	707.1	516.0
	Geometric CV (%)	12.9	11.5	29.8	28.2	32.0	36.6
$C_{min,ss}$ (ng/mL)	Minimum	133.3	115.4	139.1	160.3	168.0	115.4
	Maximum	163.1	220.3	264.4	403.5	348.1	403.5
	Median	147.1	174.6	227.9	226.2	207.4	205.1
	Arithmetic mean	147.7	177.3	210.9	235.5	225.3	210.2
	Arithmetic CV (%)	9.6	23.9	26.7	31.8	26.9	30.7
	Geometric mean	147.2	172.9	204.0	225.7	219.3	201.5
	Geometric CV (%)	9.6	26.4	29.5	30.6	24.6	29.6

Furthermore, PK in target population was characterised using the popPK model, where the influence of age on absorption rate was observed, i.e., the absorption rate appears to increase with increasing age. In the D120 responses the applicant has provided a broader discussion to justify exclusion of age as a critical covariate. The method used for simulations is generally well described and considered suitable. It could be agreed that simulated results demonstrate minimal impact on Cmax and AUC among different age groups, and, thus, it is agreed that the impact is negligible.

PK in special populations

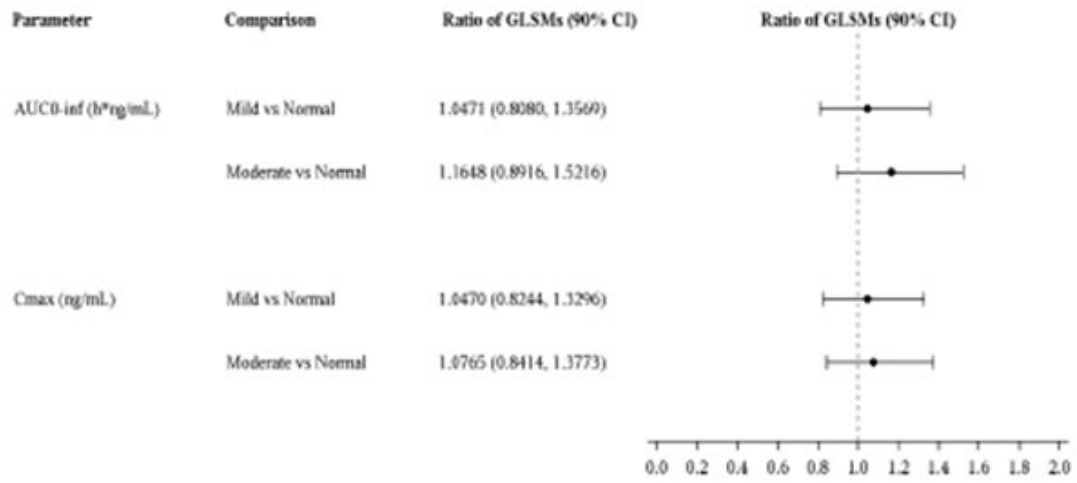
Impaired renal function

With the D180 responses the applicant has submitted the final clinical trial report for the renal impairment trial OR-ARI-REN-01. For the results, please refer to the clinical safety part, section 3.3.9.11. "Additional data provided in D180 responses".

Impaired hepatic function

The effect of hepatic impairment on the pharmacokinetics of arimoclomol following a single dose of 248 mg arimoclomol was investigated in an open-label, parallel-group, single-dose trial (OR-ARI-HEP-0) in twenty-four male and female subjects with mild and moderate hepatic impairment.

Figure 3-6 **Impact on Hepatic Impairment in the Single-dose Pharmacokinetics of arimoclomol – Trials OR-ARI-HEP-01**



CI = confidence interval; GLSM = geometric least squares mean
Source: [OR-ARI-HEP-01, Table 14.2.1-3]

Table 6-6 **Intrinsic Factor Pharmacokinetic Trials**

Trial	Ari Dose	Analyte / Matrix	N	Day	$AUC_{0\text{-}8}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ [a] (ng·h/ mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	CL/F (L/h)
OR-ARI-HEP-01	248 mg SD, Mild hepatic	Ari /Plasma	8	1	5774 (27.2)	7939 (31.0)	1420 (32.9)	1.0 (0.5,2.0)	4.75 (21.1)	31.3 (31.0)
	248 mg SD, Moderate hepatic	Ari /Plasma	8	1	5533 (21.2)	8683 (18.3)	1346 (25.5)	2.0 (0.5,6.02)	4.92 (18.7)	28.5 (18.3)
	248 mg SD, Normal hepatic	Ari /Plasma	8	1	5477 (29.1)	7505 (35.5)	1290 (30.2)	1.25 (1.0,2.5)	4.44 (18.0)	33.1 (35.5)
	248 mg SD, Mild hepatic	M2 /Plasma	8	1	3730 (31.8)	7640 (44.7)	665 (31.4)	4.0 (3.0,6.05)	6.22 (30.7)	-
	248 mg SD, Moderate hepatic	M2 /Plasma	8	1	3150 (65.1)	9350 (52.3)	673 (42.0)	6.0 (4.0,8.0)	8.75 (57.9)	-
	248 mg SD, Normal hepatic	M2 /Plasma	8	1	3280 (21.2)	6920 (30.8)	618 (20.0)	5.0 (4.0,8.0)	6.33 (35.3)	-

Trial	Ari Dose	Analyte / Matrix	N	Day	AUC_{0-8} (ng·h/mL)	AUC_{0-inf}[a] (ng·h/ mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	CL/F (L/h)
	248 mg SD, Mild hepatic	M105 /Plasma	8	1	67.7 (198)	1330 (111)	48.7 (79.6)	24.00 (11.97, 24.13)	NC	
	248 mg SD, Moderate hepatic	M105 /Plasma	8	1	NC	475 (160)	21.6 (81.2)	24.00 (4.00, 24.08)	NC	
	248 mg SD, Normal hepatic	M105 /Plasma	8	1	133 (101)	2830 (33.6)	90.7 (38.3)	24.00 (24.00, 24.03	NC	
OR-ARI-REN-01 Ongoing, results pending	248 mg SD, Mild renal	Ari /Plasma	8	1						
	248 mg SD, Moderate renal	Ari /Plasma	8	1						
	248 mg SD, normal renal	Ari /Plasma	8	1						

[a] For M105 AUC_{0-t}

AUC_{0-inf}=area under the plasma concentration-time curve from zero to infinity, AUC_{0-8}=area under the plasma concentration-time curve from zero to eight hours postdose, CL/F=oral clearance, C_{max}=maximum observed plasma concentration, $t_{½}$=apparent elimination half-life, t_{max}= time to maximum observed concentration, V_z/F=apparent volume of distribution.

Note: Geometric mean and geometric %CV are presented for all parameters except for t_{max}, for which median and minimum, maximum is presented.

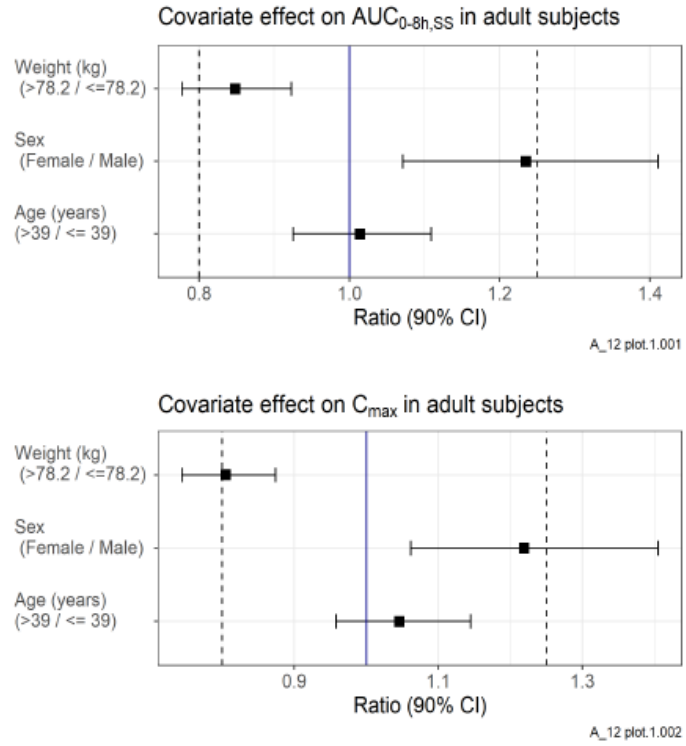
Note: All mean AUC and C_{max} values are multiplied with 0.620241 for conversion to arimoclomol base.

- **Effect of Sex, Weight, Age, and Race**

The potential impact of various intrinsic factors, including age, gender, race and bodyweight have been examined by the use of population PK analyses.

Arimoclomol C_{maxss} is 19% lower and $AUC_{(0-8)ss}$ 15% lower in subjects with body weight above the median of 78.2 kg vs. subjects with a body weight equal to or below 78.2 kg. The weight range in the clinical studies is wide (11.7-114.2).

Figure 3-4 **Impact of Age, Sex, and Weight on the Multiple Dose Pharmacokinetics of Arimoclomol - Population Pharmacokinetic Analysis in Adults, C_{max} (top) AUC_{0-8} (bottom)**



Source: [popPK report, Figure I-1 and I-2].
Filled squares indicate calculated ratio (alternative/reference) of geometric means of $AUC_{0-8h,ss}$ (upper figure) and C_{max} (lower figure) with 90% CI displayed as error bars

The combined dataset did not include enough data to evaluate the effect of **race** on the exposure of arimoclomol.

3.3.1.2. Pharmacodynamics

No dedicated PD studies have been conducted. PD proof-of-concept was evaluated in non-clinical studies. In addition, exploratory PD endpoints were included in the pivotal Phase 2/3 trial CT-ORZY-NPC-002, the design of which is described in Clinical efficacy.

Mechanism of action

Arimoclomol is an orally available small molecule that crosses the blood brain barrier (BBB). It amplifies and sustains the cellular production of HSPs, in particular HSP70 (Heat Shock Protein 70), through prolonged activation of HSF1 and induction of the HSR. HSP70 and other HSPs are critical to correct folding and processing of the integral lysosomal membrane protein NPC1, including the specific I1061T misfolding mutation, which is the most common form of mutated NPC1 in patients suffering from NPC. The HSR is linked directly to lysosomal integrity through HSP70 mediated stabilisation of lysosomal membranes and protection from cell death.

Thus, by amplifying the HSR, arimoclomol targets both protein misfolding and lysosomal dysfunction through a natural cellular defence mechanism. Arimoclomol therefore has a novel mechanism of action targeting the fundamentals of NPC aetiology: NPC protein misfolding and lysosomal dysfunction.

Primary pharmacodynamics

Primary pharmacology proof-of-concept was based on non-clinical studies with human biomaterials. Briefly, studies in NPC patient-derived fibroblasts and in -/- NPC mice, which is the most used animal

model for NPC, have been conducted. The dose dependant (50, 100, 200, 400 µM) increase in NCP1 protein was observed in all eight tested NPC patient fibroblast cell lines carrying different mutations which were also found in phase 2/3 clinical trials, including I1061T, which is the most abundant missense mutation in NPC. *In vivo* studies in -/- NPC mice demonstrated that brain HSF1 and HSP70 were upregulated in response to arimoclomol treatment.

PD markers were assessed as exploratory endpoints in the clinical study the CT-ORZY-NPC-002, the design of which is described in Clinical efficacy section. Chosen PD endpoints which are described in detail below, are considered relevant as they are important markers for NPC.

Three key biomarkers were evaluated: HSP70, un-esterified cholesterol, and cholestane-triol. Additional biomarkers evaluated were glycosphingolipids (GM3) and nLc4. A significant influence of arimoclomol exposure was identified for the change in GM3 levels in PBMC (based on $AUC_{0\text{-}8,ss}$ and $C_{max,ss}$), where a higher exposure was associated with a decrease in GM3. No influence of arimoclomol exposure was identified for any of the other biomarkers analysed.

The mean HSP70 increase was higher in patients treated with arimoclomol compared to placebo during the 12 months treatment as measured in PBMCs; a mean increase in un-esterified cholesterol level in PBMCs was observed in both placebo and arimoclomol treated patients over 12 months. However, the mean increase, and hence accumulation, of un-esterified cholesterol was considerably lower in the arimoclomol group compared to the placebo group. Cholestane-triol levels in serum declined more in the arimoclomol treated patients compared to the placebo treated patients at 12 months.

Secondary pharmacodynamics

In the studies OR-ARI-TQT-01, AALS-005 and AALS-010 the effects of arimoclomol on cardiac repolarisation, mood and alertness and renal function have been investigated, respectively. There was a correlation between arimoclomol exposure and serum creatinine increase, which can be explained by the fact that arimoclomol is an inhibitor of the OCT-2 transporter, which is involved in creatinine clearance in the kidney. All further information concerning the safety of arimoclomol is located in section 4 of this assessment report.

PD interactions with other medicinal products

No clinical PD interaction studies were conducted. Neither were the possible PD interactions discussed in the dossier.

Exposure-response analyses

The relationships between steady state exposure ($AUC_{0\text{-}8h}$) and efficacy/tolerability of arimoclomol was assessed in all patients with NPC from the CT-ORZY-NPC-002 trial. Patients received weight-adjusted daily doses ranging from 31 to 124 mg to the estimated equivalence of 372 mg/day for adults with the body weight of 70 kg.

The population covariate PK model was used to simulate exposure variables $AUC_{0\text{-}8h,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for the 34 subjects in CT-ORZY-NPC-002 who contributed to the exposure-response analysis. The objectives of the analysis were to explore whether changes in the 5-domain NPCCSS (5NPCCSS) from baseline in actively treated patients of trial CT-ORZY-NPC-002 is related to arimoclomol exposure, to explore whether changes in PD biomarkers from screening in actively treated patients of trial CT-ORZY-NPC-002 is related to arimoclomol exposure, to test whether arimoclomol exposure in actively treated patients of trial CT-ORZY NPC-002 is a predictor of changes in serum creatinine throughout treatment.

Based on the exposure-response analysis, it was concluded that trajectories of 5-domain NPCCSS tend to be approximately linear. Linear mixed-effects modelling was used to develop a base model

(RunNPC003), which include a slope parameter with associated inter-individual variability, that adequately describes the observed 5-domain NPCCSS trajectories.

Analysis of exposure variables and covariates for their influence on the slope parameter revealed that co-administration of miglustat was associated with a sizeable decrease in the slope. The association was statistically highly significant and accounted for 92% of the variance of the inter-individual variability in the slope. Once the influence of miglustat co-administration had been included in the model, increased exposure variables and height showed some association with decreasing the slope parameter. While the effects did achieve statistical significance, none were formally accepted due to concerns about significant correlation between exposure variables and body size covariates (age, weight, and height), and also association between many of these variables and co-administration of miglustat, the use of which was not randomised in the CT-ORZY-NPC-002 trial. Beyond co-administration of miglustat, no further covariate influence(s) could be declared robustly.

A significant influence of arimoclomol exposure was identified for the change in GM3 levels in PBMC (based on $AUC_{0\text{-}8,ss}$ and $C_{max,ss}$), where a higher exposure was associated with a decrease in GM3C. No influence of arimoclomol exposure was identified for any of the other biomarkers analysed.

The analysis of whether arimoclomol exposure is a predictor of changes in serum creatinine levels was conducted for changes in serum creatinine from Screening to Visit 2 (approximately 2 weeks of treatment). On average, there was a rapid increase in serum creatinine (of approximately 7 µmol/L above screening level) soon after the start of treatment, which was maintained throughout the rest of the trial. The influence of covariates and exposure variables on the change in serum creatinine from screening to Visit 2 was analysed. While there is clearly an effect of arimoclomol treatment on serum creatinine, the analysis could not identify a statistically significant influence of arimoclomol exposure on changes in serum creatinine in the patients treated with arimoclomol.

PopPK exposure-response analysis

Numerical integration of the Run030 popPK model was used for the simulation of exposure variables for all subjects contributing data to the ER analysis. PopPK model development is described previously and it was used for PK analysis, it is based on data from 134 subjects of age 2-76 years from six clinical studies (40338, AALS-001, AALS-005, AALS-010, NPC-002 and OR-ARI-MET-01 (ORARIMET).

The individual exposure variables were obtained from steady-state PK profile simulations (after the sixth dosing interval with regular 8 hourly dosing), which are based on the patient's assigned dose at randomisation and the patient's individual PK parameters. The simulated individual exposure variables for arimoclomol were: the AUC over the dosing interval at steady-state ($AUC_{(0\text{-}8)ss}$), the maximum plasma concentration at steady-state (C_{maxss}), and the minimum plasma concentration at steady-state (C_{minss}).

Analysis of exposure variables and covariates for their influence on the slope parameter revealed that co-administration of miglustat was associated with a sizeable decrease in the slope.

A graphical analysis and a quantitative covariate search, identified co-administration of miglustat as the most significant influence on SLP (RunNPC016) such that the population estimate of SLP is reduced from 5.19 5NPCCSS/year (90% CI 2.92 to 7.46) without miglustat co-administration to 0.0217 5NPCCSS/year (90% CI -0.421 to 0.465) with miglustat, where co-administration of miglustat accounts for 92% of the variance of IIV in SLPOnce the influence of miglustat co-administration had been included in the model, increased exposure variables and height showed some association with decreasing the slope parameter.

Changes in seven PD biomarkers from screening to Visits 4 and 6 were analyzed for the influence of covariates and exposure variables. The only biomarker where a significant influence of arimoclomol

exposure was identified was the change in GM3 in peripheral blood mononuclear cells (ΔGM3C). The significant influence was for both the Visit 4 and Visit 6 data, and at both visits the significant exposure variables were $AUC_{(0-8)ss}$ and C_{maxss}. The directionality of the influence is such that more negative ΔGM3C is associated with higher exposure.

Beyond co-administration of miglustat, no further covariate influence(s) could be declared robustly.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of arimoclomol were demonstrated to be linear with increasing dose rates, and stable over the time course of treatment.

Arimoclomol exhibit dose-proportional pharmacokinetics with an oral bioavailability of at least 42%. The absolute bioavailability of arimoclomol in humans was not investigated. In rats the absolute bioavailability of arimoclomol following oral administration was 84% and 75 % in dogs relative to arimoclomol i.v. administration (based on AUC0-inf).

Peak plasma concentration is reached within 0.25 to 3.0 hours (tmax). Food does not seem to have a relevant effect on pharmacokinetics. The effect of a high fat meal on the pharmacokinetics of 62 mg arimoclomol was determined in Trial AALS-004 and AALS-011. The 90% CI for the AUC0-t and AUC0-inf, and Cmax ratios were within the limits of 80% to 125% in both studies. The median tmax was increased twofold in the fed versus the fasted state (3.0 versus 1.5 hours). However, since Miplyffa is considered for long term use, the difference in tmax is, not deemed clinically relevant.

The mean volume of distribution at steady state (V/F) is approximately 200-300 L, which indicates extravascular distribution. Arimoclomol crosses the blood-brain-barrier as suggested by the dose-dependent increase in mean arimoclomol cerebrospinal fluid (CSF) concentrations in patients with ALS. Protein binding of arimoclomol is low (approximately 10%), and binding appears to be independent of arimoclomol plasma concentrations.

Arimoclomol is eliminated by both renal clearance and by metabolism. The mean CL/F of arimoclomol is approximately 40 L/h, and the apparent elimination half-life is approximately 4 hours. Following three times daily doses, arimoclomol accumulated 1.3 to 1.4-fold consistent with the elimination half-life and dosing frequency.

After a single oral dose of 14C-arimoclomol, 89.5% of drug-related material is recovered with 77.5% recovered in urine and 12% in faeces.

Arimoclomol is metabolised by several routes and the three dominant pathways are glutathionation, O-glucuronidation and NO-cleavage. The most abundant metabolites circulating in plasma are the cysteine-conjugate of arimoclomol (M2) formed following hydrolysis of the glutathione-conjugate, the arimoclomol O-glucuronide (M5) and the cleavage product M105. Based on the *in vitro* pharmacology studies (induction of HSP70 mRNA in HeLa cells following heat shock and induction of NPC1 protein in human fibroblast cells) and their plasma exposures, none of the abundant metabolites M2, M5, or M105 is expected to contribute to the observed pharmacological effects of arimoclomol. Pharmacokinetic parameters of the most abundant metabolites M2, M5, and M105 have been investigated in 6 healthy volunteers following quantification of the metabolites in plasma and urine (OR-ARI-MET-01). Additionally, PK of arimoclomol and the metabolites M2 and M105 were investigated in a TQT trial (OR-ARI-TQT-01) in 34 healthy male subjects. The trial was completed in December 2020 and was submitted to EMA together with the responses to the D120 LoQ. Metabolite M5 was not investigated in the trial as it is an O-glucuronide and not of toxicological concern (ICH 2012). The results of the TQT trial constituted a negative TQT study according to the ICH E14 guidance.

Furthermore, arimoclomol did not impact heart rate or cardiac conduction in the subjects in the trial and was well tolerated by the subjects at both the therapeutic (372 mg/day) and the supratherapeutic (1116 mg/day) doses. When compared to the hepatic trial (OR-ARI-HEP-01), where subjects received a single dose of 248 mg arimoclomol, both the therapeutic and supratherapeutic doses were higher and the subjects were exposed to multiple doses.

The PK profiles of arimoclomol, M2 and M105 were captured after single and multiple doses of arimoclomol. The maximum observed plasma concentration was 6900 ng/mL for arimoclomol citrate, 2270 ng/mL for M2 and 833 ng/mL for M105. The mean arimoclomol citrate exposure over the dose interval of 8 hours (AUC0-8) increased from 5610 h*ng/mL after the therapeutic 124 (200) mg dose, to 18400 h*ng/mL after the supratherapeutic 372 (600) mg dose, both on Day 3. Therefore, a three-fold increase in dose level resulted in an at least 3 times higher mean exposure of arimoclomol citrate. The mean terminal half-life (t1/2) of arimoclomol citrate in plasma on Day 3 was similar for the therapeutic and the supratherapeutic dose of arimoclomol (4.43 (11.6%) and 4.19 (9.7 %) hours, respectively). The metabolite M2 showed a slightly longer t1/2 (5.63 (10.4%) for the therapeutic dose and 5.40 (10.0%) for the supratherapeutic dose, as observed on Day 3 than arimoclomol citrate. The t1/2 for M105 could not be calculated as the terminal elimination phase for M105 plasma profile was not reached on Day 1 or Day 3 for neither the therapeutic nor the supratherapeutic arimoclomol dose. While the Day 1 plasma profiles showed rising M105 during the first dose interval of 8 hours, the Day 3 M105 profiles after t.i.d. dosing of both the therapeutic and supratherapeutic doses of arimoclomol show that M105 metabolite reached a steady state.

In conclusion the TQT trial including a total of 34 healthy male subjects showed no safety concerns after multiple doses of arimoclomol up to 1116 mg/day and where the exposure to both metabolites (M2 and M105) reached a steady state.

Consequently, based on the results from the TQT trial no potential safety issue could be seen related to the metabolites and thus a dose reduction in patients with hepatic impairment may not be warranted.

The pharmacokinetic analysis suggested that age did not have a significant effect on the pharmacokinetics of arimoclomol in adults. However, the popPK model has estimated Ka value around 0.338 h with CV= 48.5% and age was suggested as important factor for absorption. Provided simulations by applicant demonstrate that Ka has minimal impact on Cmax and AUC among different age groups, and thus it is agreed that expected impact is negligible.

Sex and body weight (BW) were found to be significant covariates affecting the exposure of arimoclomol in adults. This effect might be related to the fixed dosing regimen in adults, with increased clearance with increasing body weight, and with women generally having a lower body weight than men. In the pivotal Phase 2/3 CT-ORZY-NPC-002 trial, subjects with body weight between 8 and 55 kg were dosed per body weight in pre-defined weight bands. Subjects above 55 kg received a fixed dose level of 124 mg t.i.d. arimoclomol. The observed effects of sex (AUC0-8: 24%) and body weight (AUC0-8: 15%, body weight below and above 78 kg) in adults are modest and not considered to be clinically relevant. Consequently, no dose adjustment of arimoclomol based on sex or age is necessary. The same fixed dosing regimen can be administered to all patients weighing > 55 kg.

The effect of race on the exposure of arimoclomol has not been studied.

Three dose forms were used in the Phase 2/3 trial CT-ORZY-NPC-002 (capsule, capsule emptied and dosed with food or drink, capsule emptied and dosed using gastric tube) to support administration in a population comprising paediatric patients and patients with swallowing difficulties. Thereof it was investigated whether these different dose forms could have an influence on the absorption rate (Ka). According to the applicant the analysis of the POP PK revealed that any influence of dose form was small and of no clinical relevance.

During the clinical development of arimoclomol for NPC, the drug product formulation has been modified with respect to the quantitative composition of the excipients. For the blinded phase of the clinical Phase 2/3 trial, CT-ORZY-NPC-002, a capsule formulation with excess amount of excipient material for the lower capsule strengths was required in order to ensure blinding. The capsule formulation was then modified between the blinded and the open label (OL) phase of the CT-ORZY-NPC-002 trial in order to optimise it for the patients by reducing the capsule fill weight and the amount of excipients to be taken with each capsule. Furthermore, the gelatine capsule shell was replaced with a shell of hydroxypropyl methyl cellulose (HPMC).

To further ease compliance and avoid the ingestion of multiple capsules three times a day, a specific capsule strength for each recommended dose has since then been developed for the to-be-marketed product covering each of the 5 weight bands. Consequently, the quantitative composition of the excipients was modified slightly for some of the strengths between the OL phase of the CT-ORZY-NPC-002 trial and the to-be-marketed product. In order to justify the use of the different drug product formulations used during the clinical development of arimoclomol for NPC and the to-be-marketed formulation, a biowaiver for bioequivalence studies is requested based on the BCS (Biopharmaceutics Classification System) approach. Generally, applying for a BCS-based biowaiver is restricted to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III) and known not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

The BCS prerequisite regarding high solubility has been demonstrated for Arimoclomol citrate under conditions as requested in the respective Guidelines (BE Guideline ICH9). Regarding permeability the applicant was asked to provide further data in order to clarify the BCS class for arimoclomol (BCS Class I or III). In its response the applicant provided data of a recently completed *in vitro* permeability study, using a validated Caco-2 test system and bioanalytical LC-MS method. Permeability was compared to the high and moderate permeability model drugs, minoxidil and atenolol, respectively. In this study, the *in vitro* cell line permeability for arimoclomol was similar to the highly permeable model drug minoxidil. Furthermore, the applicant was requested to provide information on possible excretion of arimoclomol or its metabolites in faeces by bile and whether unchanged drug contributes to the 12% recovered material in faeces. The applicant responded that stability studies have shown that arimoclomol is stable in gastric and intestinal fluids and as a consequence, the drug related material collected in faeces is expected to have its origins from arimoclomol that has previously been absorbed. Additionally, in bile cannulated animals, the amount of drug related material excreted in bile was similar to the amount excreted in faeces in intact animals, which further indicates complete absorption of the oral dose of arimoclomol. Based on the data provided it was agreed that arimoclomol meets the requirements for high permeability which supports its designation as a BCS Class 1 drug.

To qualify for a BCS-based biowaiver for BCS Class I drug substances both the test product and reference product should display either very rapid (≥85% for the mean percent dissolved in ≤ 15 minutes) *in vitro* dissolution characteristics, or rapid (≥85% for the mean percent dissolved in ≤ 30 minutes) and similar *in vitro* dissolution characteristics (i.e., based on f2 comparison).

For the reference product, both the 31 mg and the 62 mg dosage strength clearly showed very rapid dissolution characteristics.

For the test products, the 31 mg, 47 mg and 124 mg capsule strengths all dissolved in average 85% or more of the label claim of the drug within 15 minutes in all three dissolution media.

For the test product at 62 mg dosage strength, in average 85% or more of the label claim of the drug dissolves within 15 minutes at pH 1.2 and 4.5.

For the 93 mg dosage strength, where in average 85% or more of the label claim of the drug is dissolved within 15 minutes at pH 4.5 and 6.8.

Of note, test product batches of 62 mg and 93 mg dosage strengths failed to meet the criterion of ≥ 85% dissolved within 15 minutes at pH 6.8 and 1.2, respectively. Thus, the applicant was asked to demonstrate similarity of the profiles by calculating the similarity factor f2 or in case $f2$ statistic is not suitable to use alternative methods according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Some prerequisites for the f2 comparison were not met in this case and due to fundamental differences in the early dissolution time points, also other attempts to show similarity using alternative methods, e.g., bootstrap methodology were invalid. The applicant claimed that the data provided are indicating that the two dissolution results at 84% are a result of the variability in the disintegration time of the HPMC shell rather than intrinsic properties of the capsule formulation per se.

It is acknowledged that dissolution methods are often affected by the insufficient hydrodynamics in dissolution vessels (Lozano et al., 1994) and fragments of the shell may sometimes trap the powder against the bottom of the vessel, hindering fast and complete release of the drug (Sherry et al., 2010). According to ICH M9, the use of the basket apparatus at 100 rpm is recommended when high variability or coning is observed in the paddle apparatus at 50 rpm (or at 75 rpm in this case). Therefore, the applicant was asked to further discuss, why this approach has not been followed. The applicant responded that as part of the dissolution method development, a comparison of Ph. Eur. Apparatus 1 (baskets) and Apparatus 2 (paddles) was performed. The results showed that the dissolution was even further delayed using Apparatus 1 at 100 rpm, indicating insufficient hydrodynamics in the dissolution vessel. This was further substantiated by the coning that was visually observed during the test. In conclusion, the applicant considered the use of Apparatus 2 at 75 rpm. The arguments of the applicant can be followed and the issue is not further persued.

Pharmacodynamics

Primary pharmacology proof-of-concept was based on non-clinical studies with human biomaterials. Briefly, studies in NPC patient-derived fibroblasts and in -/- NPC mice, which is the most used animal model for NPC, have been conducted. The dose dependant (50, 100, 200, 400 µM) increase in NCP1 protein was observed in all eight tested NPC patient fibroblast cell lines carrying different mutations which were also found in phase 2/3 clinical trials, including I1061T, which is the most abundant missense mutation in NPC. *In vivo* studies in -/- NPC mice demonstrated, that brain HSF1 and HSP70 were upregulated in response to arimoclomol treatment.

There were no dedicated PD studies, but PD markers are assessed as exploratory endpoints in the clinical study the CT-ORZY-NPC-002, the design of which is described in Clinical efficacy section. Chosen PD endpoints which are described in detail below, are considered relevant as they are important markers for NPC.

Three key biomarkers were evaluated: HSP70, un-esterified cholesterol, and cholestane-triol. Additional biomarkers evaluated were glycosphingolipids (GM3) and nLc4. A significant influence of arimoclomol exposure was identified for the change in GM3 levels in PBMC (based on $AUC_{0\text{-}8,ss}$ and $C_{max,ss}$), where a higher exposure was associated with a decrease in GM3. No influence of arimoclomol exposure was identified for any of the other biomarkers analysed.

The mean HSP70 increase was higher in patients treated with arimoclomol compared to placebo during the 12 months treatment as measured in PBMCs; a mean increase in un-esterified cholesterol level in PBMCs was observed in both placebo and arimoclomol treated patients over 12 months. However, the mean increase, and hence accumulation, of un-esterified cholesterol was considerably lower in the

arimoclomol group compared to the placebo group. Cholestane-triol levels in serum declined more in the arimoclomol treated patients compared to the placebo treated patients at 12 months.

The applicant has explained that no robust exposure-response association was possible from the small amount of data available on pharmacodynamic marker HSP70, as a result of loss of samples. As for Unesterified (UE) Cholesterol and Cholestane-triol, it was explained that these are biomarkers of mechanism of disease and, as such, might not show direct correlation with exposure, which is agreed on.

Together with the responses to Day 120 List of Questions, the applicant has provided new analysis on Lysosphingomyelin-509 (Lyso-SM-509) which was recommended by CHMP in the SA as additional highly sensitive and specific biomarker. Results demonstrate reduction of Lyso-SM-509 in response to arimoclomol exposure, although there is high interindividual variability. Regression analysis of relative change in Lyso-SM-509 against arimoclomol plasma exposure ($AUC_{0\text{-}8h,ss}$) shows reduction in Lyso-SM-509 in association with arimoclomol treatment with a correlation with exposure at 6 (p=0.0329) and 12 (p=0.0154) months. However, individual study results indicate that in some of the patients, Lyso-SM-509 levels appeared to be higher either at 6 or 12 months or at both time points when compared to baseline. Measured concentrations and the % change from baseline for the 10 patients has been presented with the D180 responses; it was clarified that some minor increases may be due to analytical variation. It has been noted that, in 5 patients, a tendency towards a slight increase over time is seen, but all parameters are randomly distributed, and no clear trend can be seen with regards to withdrawal, patient age at inclusion, age at onset of NPC symptoms, years of disease etc. The applicant speculates that Lyso-SM-509 might be a potential biomarker for disease progression, although the specific biomarker Lyso-SM-509 was included to assess a treatment effect of arimoclomol and to explore a positive effect of arimoclomol on the lipid burden, not to evaluate disease progression. Additional data are collected during open label extension phase of the trial and will be provided with the final clinical study report.

While it has been stated that assessment of biomarkers should be considered as a first-line test to screen for NPC (Geberhiwot, et al, 2018), it could be agreed with the applicant that these markers reflecting disease pathology may not necessarily show a direct correlation with exposure to arimoclomol as changes (fluctuations) in their levels during the natural course of the disease are more complex and influenced by various biological factors. This might be the reason behind the unability of the presented biomarker data to strongly support a suggested mechanism of action and, thus, therapeutic efficacy. However, the data on some biomarkers, e.g., cholestane-tiol, unesterified cholesterol, Lyso-SM-509 and GM3 suggest some potential effect of arimoclomol treatment, but data are not sufficient to draw any firm conclusions.

In the studies OR-ARI-TQT-01, AALS-005 and AALS-010 the effects of arimoclomol on cardiac repolarisation, mood and alertness and renal function have been investigated, respectively. There was a correlation between arimoclomol exposure and serum creatinine increase, which can be explained by the fact that arimoclomol is an inhibitor of the OCT-2 transporter, which is involved in creatinine clearance in the kidney. All further information concerning the safety of arimoclomol is located in section 4 of this assessment report.

The applicant has provided discussion on the potential of metabolism and transporter mediated interaction and on potential off target effects. It is agreed that the likelihood of clinically relevant metabolism-, transporter- and pharmacodynamic mediated drug-drug interactions as well as possible off-target effects is low.

In order to describe the relationship between dose and effect, the applicant provided data from the clinical study CT-ORZY-NPC-002, in which the relationships between steady state exposure ($AUC_{0\text{-}8h}$) and efficacy/tolerability of arimoclomol was assessed in all patients with NPC. The modelling approach

based on previously developed popPK model have been used to explore PD data relationship with exposure (PK) data. The objectives of this exposure-response analysis were to find whether changes in the 5-domain NPCCSS (5NPCCSS) and PD biomarkers from baseline in actively treated patients during blinded phase of study NPC-002 is related to arimoclomol exposure. In general, the statistically significant connection between exposure and PD biomarkers has not been established. The graphical analyses suggest that there could be expected a mean increase in 5NPCCSS from baseline of approximately 0.7 unit after one year of treatment, while the exposure response analyses does not demonstrate convincing evidence. It is hard to have any confidence in estimates for the association between change in 5-domain NPCCSS from screening and arimoclomol exposure based on popPK methods, as the strong association between miglustat co-administration and arimoclomol exposure is observed, which does not allow to make any judgment on single administrated arimoclomol PD effects in patients. Based on current data, arimoclomol co-administration with miglustat should be considered.

3.3.3. Conclusions on clinical pharmacology

- The biomarker data from the CT-ORZY-NPC-001 and -002 trials are not fully convincing to meaningfully support clinical efficacy data.
- One open issue regarding deviation from the methods according to the respective guidelines (ICH M9 and Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) used in the *in vitro* dissolution study performed in support of the BCS-based biowaiver needs to be clarified.
- The presented programme for testing of PD and PK/PD is overall acceptable and is considered supportive for the targeted indication and therapeutic approach.

3.3.4. Clinical efficacy

The efficacy evaluation of arimoclomol in the treatment of NPC is based on:

- One supportive, prospective, observational trial (CT-ORZY-NPC-001) with no arimoclomol administered to characterise the individual patient disease progression profile.
- One randomised, placebo-controlled trial (CT-ORZY-NPC-002) consisting of a double-blind treatment phase (completed) evaluating efficacy and safety and including follow-up in an ongoing open-label extension phase for up to 48 months of treatment evaluating long-term safety and efficacy. In addition, trial CT-ORZY-NPC-002 includes an ongoing (recruitment currently paused) sub-study in patients aged 6 months to <2 years, where all patients receive arimoclomol, evaluating safety and tolerability in this age group.

The trials contributing to the efficacy evaluation are summarised in the table below.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
CT-ORZY-NPC-001	12 sites in 7 countries: 1 – Denmark, 2 – Germany, 4 – Italy, 1 – Poland, 1 – Spain, 1 – Switzerland, 2 – United Kingdom	Observational, multisite, multinational study	Not applicable, routine clinical care, majority (n=30; 83.3%) treated with Miglustat	to characterise disease progression in patients with NPC	36 patients altogether	follow-up 6-14 months	2 to 18 years of age, mean age 9.86, male / female 15 / 21	confirmed diagnosis in NPC1 or NPC2	5-domain NPCCSS NPC (Niemann Pick Disease Type C) Clinical Severity Scale
CT-ORZY-NPC-002	14 sites in 9 countries: 1 – Denmark, 2 - France, 2 – Germany, 2 – Italy, 1 – Poland, 1 – Spain, 1 – Switzerland, 2 – United Kingdom, 2 – United States	Phase 2/3 double-blind, randomised, placebo-controlled, multisite, multinational trial	Arimoclomol 372 mg/day (weight-adjusted)	to evaluate the therapeutic response and safety of arimoclomol versus placebo when administered in addition to routine clinical care in patients with NPC	double-blind phase - 34 patients received Arimoclomol and 16 patients – placebo; 41 patients - open-label extension phase (Ari-Ari – 26, Pbo-Ari – 15)	12 months of double-blind treatment followed by up to 48 months of open-label extension (for the current submission – 12 months)	2 to 18 years of age; double-blind phase mean age 11.1 years, male / female trial group 17 / 17, placebo – 7 / 9; open-label phase mean age 12.3 years, male / female Ari-Ari group 13 / 13, Pbo-Ari group 7 / 8	participation in the previous study NPC-001 (27 out of 36 continued) or confirmed diagnosis in NPC1 or NPC2	5-domain NPCCSS NPC (Niemann Pick Disease Type C) Clinical Severity Scale

Dose-response studies and main clinical studies

The evidence for the clinical efficacy of arimoclomol in NPC at the proposed dose is based on 1 Phase 2/3, placebo-controlled trial, CT-ORZY-NPC-002. No dose finding trial was conducted.

The dose of arimoclomol in trial CT-ORZY-NPC-002 was chosen in order to ensure an adequate nonclinical safety ratio.

The dose was calculated based on the patient's body weight (BW) and ranged from 93 to 372 mg/day as illustrated in Table 4-2. The administered dose was scaled to be equivalent to 372 mg/day for adults (with BW = 70 kg). Based on the half-life of arimoclomol of approximately 4 hours, three times daily dosing was applied to maintain a sustained plasma exposure throughout the day.

Table 4-1 Arimoclomol Dosing Based on Patient BW – CT-ORZY-NPC-002

Patient Body Weight (BW)	Investigational Medicinal Dosing (IMP) Dose
8-15 kg	31 mg t.i.d. (93 mg/day)
>15-22 kg	47 mg t.i.d. (140 mg/day)
>22-38 kg	62 mg t.i.d. (186 mg/day)
>38-55 kg	93 mg t.i.d. (279 mg/day)
>55 kg	124 mg t.i.d. (372 mg/day)

Main study(ies)

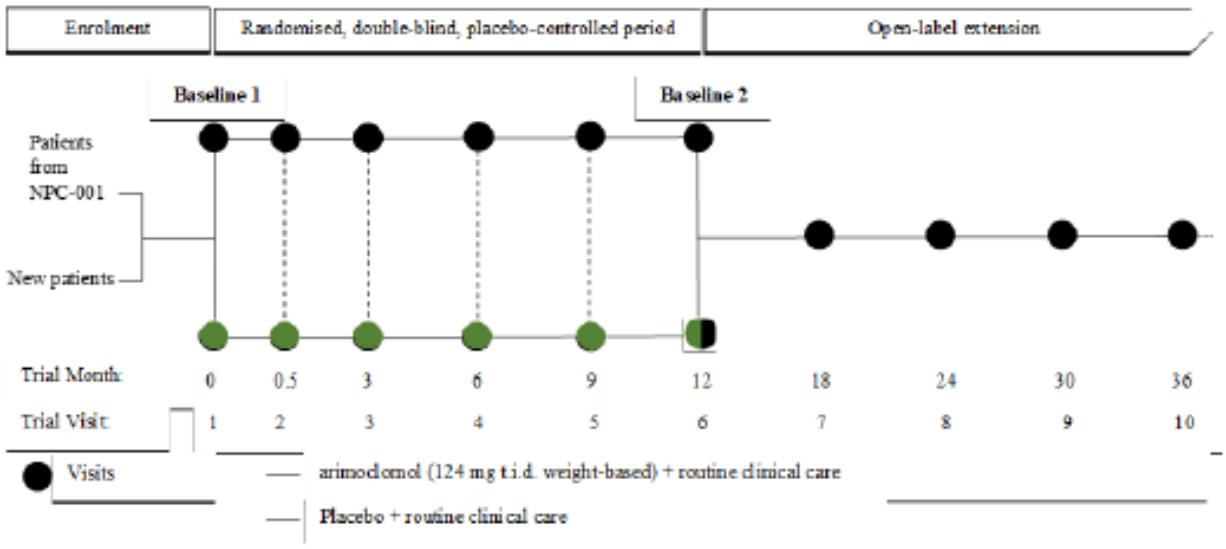
CT-ORZY-NPC-002 (Phase 2/3) Double-blind Phase and Open-label extended Phase

Methods

CT-ORZY-NPC-002

The design of trial CT-ORZY-NPC-002 is presented in Figure 9-1; showing the double-blind treatment phase, where patients with NPC were randomised to either arimoclomol or placebo treatment, followed by the open-label treatment phase, where all patients received arimoclomol.

Figure 9-1 Trial Design



Notes:

- In the open-label extension, all patients, i.e., those randomised in the double-blind phase to arimoclomol (arimoclomol-arimoclomol group) and those to placebo (placebo-arimoclomol group) received arimoclomol.
- Throughout the trial, patients stayed on their ongoing prescribed routine clinical care, including miglustat and symptom management.

Abbreviations: t.i.d = three times a day

CT-ORZY-NPC-002 Double-blind Phase

The double-blind treatment phase of trial CT-ORZY-NPC-002 was a 12-month randomised, placebo-controlled, multi-national phase III trial in patients with NPC to assess the efficacy and safety of arimoclomol administered on top of the patient's routine clinical care (including miglustat where applicable).

The patients were randomised 2:1 to receive arimoclomol (weight-based dosing) or placebo.

Randomisation was stratified by miglustat treatment yes/no. Patients <12 years of age had an arimoclomol single-dose PK evaluation performed before (and independent of) randomisation, to confirm an acceptable exposure level.

During the 12-month treatment phase, efficacy assessments for the primary endpoint (5- domain 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. For patients participating in both trials, End of Trial (Visit 2) in the CT-ORZY-NPC-001 trial was used as baseline (Visit 1) for the CT-ORZY-NPC-002 trial.

CT-ORZY-NPC-002 Open-label Phase

The open-label extension phase of trial CT-ORZY-NPC-002 consists of a treatment period with a duration of 48 months (or until arimoclomol has received US/EU marketing authorisation), where all patients receive arimoclomol. During the extension phase, efficacy is assessed every 6 months. The open-label phase is ongoing.

Study Participants

The population consisted of male and female patients from 2 years to 18 years and 11 months of age, of any ethnicity, with a confirmed diagnosis of NPC, and at least one NPC-related neurological symptom at the time of screening. Eligible patients had either no prior miglustat treatment or were on stable dose of miglustat for at least 6 months prior to trial entry and had preserved ability to walk either independently or with assistance.

- Main inclusion criteria

  Males and females aged from 2 years to 18 years and 11 months

  and

  EITHER

  NPC patients who had entered the CT-ORZY-NPC-001 trial when aged from 2 years to 18 years and 11 months; and who had completed Visit 2 (EoT) of the CT-ORZY-NPC-001 trial.

  OR

  NPC patients who did not enter or complete the CT-ORZY-NPC-001 trial but were fulfilling all of the criteria listed below:

  - Diagnosis of NPC1 or NPC2;
  - NPC diagnosis confirmed by:
    - 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 x upper limit of normal).

- Main Exclusion Criteria:
  - Recipient of a liver transplant or planned liver transplantation
  - Severe liver insufficiency (defined as hepatic laboratory parameters, aspartate transaminase [AST] and/or alanine transaminase [ALT] greater than three- times the upper limit of normal for age and gender sex (central laboratory assessment)
  - Renal insufficiency, with serum creatinine level greater than 1.5 times the upper limit of normal (central laboratory assessment)

Treatments

In the blinded phase, arimoclomol or placebo capsules were administered orally three times a day (t.i.d.) for 12 months.

If IMP administration during the blinded phase coincided with the administration of other concomitant medication, the IMP was to be administered first.

If required, the IMP could be dissolved in 10 mL (i.e. 2 teaspoons) of liquid (water, apple juice, or milk) or in a tablespoon of soft foodstuff (yoghurt or apple sauce). In the dissolved or dispersed state, the IMP could also be administered via a gastric tube (as applicable).

The patient's weight was to be measured at each visit and the IMP dose adjusted as required.

To confirm the corresponding dose for individual patients less than 12 years of age, a single dose PK evaluation was performed by an independent assessor following a single dose of arimoclomol to verify the area under the curve in 0-8 hours (AUC0-8h).

In the event that unexpected PK profiles were obtained (from patients less than 12 years of age) which were clinically significant and could potentially impact the safety of the patient (e.g. risk of accumulation), additional PK sampling could be performed at a subsequent visit prior to randomisation and to commencing continuous dosing of IMP (arimoclomol or placebo, as per the trial randomisation).

The IMPs were capsules (arimoclomol citrate or placebo) for oral administration. The capsules were identical in appearance.

Objectives

CT-ORZY-NPC-002 Double-blind Phase

Primary Objective

- To evaluate therapeutic response to arimoclomol versus placebo, both in addition to best available standard of care, at 12 months

Secondary Objectives

- To evaluate the therapeutic response to arimoclomol through clinical, biological and imaging assessments at 6 and 12 months
- To evaluate the safety of arimoclomol

Hypothesis:

The model will be fitted with treatment, miglustat level and visit as fixed effects along with a treatment-by-visit interaction term. The estimated treatment effect will be taken from the treatment-by-visit interaction term at 12 months. The estimated treatment effect will be presented with a 95% CI and a p-value to test the null hypothesis that the effect of arimoclomol and placebo is the same

CT-ORZY-NPC-002 Open-label Phase

- To evaluate the long-term therapeutic response (clinical and biological assessments) of arimoclomol in patients with Niemann-Pick disease type C (NPC) at 18, 24, 30, and 36 months
- To evaluate the safety of arimoclomol in patients with NPC

Outcomes/endpoints

Primary efficacy endpoint

- Change in the NPC disease severity based on the 5-domain NPC Clinical Severity Scale (NPCCSS) scores (ambulation, speech, swallow, fine motor skills and cognition) from baseline

(Visit 1) to 12 months (Visit 6) (double blind phase), and from Baseline 1 and 2, respectively, at 18, 24, 30, and 36 months (OL phase).

Key secondary efficacy endpoints

- Responder analysis if Patient's Clinical Global Impression Scale of Improvement (CGI-I) score remains stable or shows improvement at 12 months (double blind), and remains stable or improves compared to Baseline 1 and 2 at 18, 24, 30, and 36 months (OL phase)
- Responder analysis if Patient's 5-domain NPCCSS score remains stable or improves at 12 months compared to baseline (double blind), and), and remains stable or improves compared to Baseline 1 and 2 at 18, 24, 30, and 36 months (OL phase)

  ("Stable" is defined as a patient's total score for the 5-domains being the same at Month 12 as at baseline. If a patient's total score at Month 12 is lower than at baseline, this is an improvement; if a patient's total score at Month 12 is higher than at baseline, this is a worsening).
- Time to worsening (as defined by reaching the minimal clinically important difference (MCID) on patient's 5-domain NPCCSS).
- Proportion of patients worsening (as defined by reaching the MCID on patient's 5-domain NPCCSS) at 6 and 12 months (double-blind) and at 18, 24, 30, and 36 months (OL phase)
- Change in full scale NPCCSS apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 12 months (double-blind), and from Baseline 1 and 2, respectively, at 18, 24, 30, and 36 months (OL phase)

Randomisation and blinding (masking)

Randomisation:

CT-ORZY-NPC-002 Double-blind Phase

At the Screening Visit, the investigator assigned a patient number to the patient.

Once the patient was considered by the investigator to be eligible for the trial, the investigator created a new patient record in the eCRF system. Patients were stratified into Strata A (on miglustat therapy) and B (not on miglustat therapy).

Upon randomisation, the IRT system assigned a randomisation number to the patient. The treatment assigned to each patient was determined according to a computer-generated randomisation list.

Hereafter, patients were randomised to receive placebo or arimoclomol with an allocation ratio of 1:2.

Blinding:

CT-ORZY-NPC-002 Double-blind Phase

As this was a double-blind, placebo-controlled trial, both the patients and the investigators were blinded to the IMP assignment and remained blinded throughout the 12-month blinded treatment phase until the final database lock (DBL).

The treatment allocation for each patient was managed via IRT and the IMP was blinded by means of treatment code lists.

To avoid possible unblinding of the investigators due to possible treatment effects, Visit 2 creatinine test results (central laboratory analysis) were reviewed by an independent expert and not sent to the

site. The independent expert contacted the investigator if further safety follow-up was required. After trial completion and unblinding of the trial data, Visit 2 creatinine test results were transferred to Orion Clinical Services Data Management for inclusion in the trial database.

The independent DSMB was provided with unblinded data as appropriate for the evaluation of safety data.

To ensure blinding, all IMPs (placebo, 25 mg, 50 mg, and 100 mg capsules) were visually indistinguishable in size and appearance. The excipient composition, texture, appearance, solubility, smell and flavour were carefully matched to mask the identity of the capsule fill, to avoid unblinding if the capsules were opened to mix or dissolve the contents into liquid or foodstuff.

To ensure blinding of the IMP packages, the number of capsules per container and all container parts were identical and from the same batches. The label batches were the same, the label print was completed on the same print station and the position of the label was applied consistently between treatment groups.

Statistical methods

Analysis sets

Full Analysis Set

The Full Analysis Set (FAS, equivalent here to mITT) was defined as those patients who were randomised and who have received at least 1 dose of randomised treatment medication (excl. single dose of arimoclomol for the assessment of PK prior to initiation of their randomised treatment). The CT-ORZY-NPC-002 Protocol defined FAS as: "The Full Analysis Set (FAS) is defined as those patients who were randomised and who have at least one post-baseline assessment of NPCCSS." Based on FDA feedback prior to unblinding (August 2018), the definition had been updated to the above. The FAS was to be used for all efficacy analyses. If any patients received the wrong treatment in error, they were to be analysed as randomised. Patients who used the escape route were to be censored at the point where they start rescue medication.

Per Protocol Set

The Per Protocol (PP) set was defined as those patients who had taken at least 80% of their study drug medication up to the 6-month assessment (Visit 4) and had an assessment at 6 months or beyond. This definition excluded all patients with less than 6 months of follow up data. The 80% of medication criterion were to be reviewed and reconfirmed at the time of the blind review of the database. Patients without a confirmed diagnosis of NPC, as confirmed by the study inclusion criteria, were to be excluded from the PP set. The PP set was planned to be used for selected efficacy analyses (see SAP). Patients who received the wrong treatment in error were to be excluded from these efficacy analyses.

Completers Analysis Set

The Completers Analysis Set (CAS) was defined as those patients who had taken at least 80% of their study drug medication up to the 12-month assessment (Visit 6) and had, as a minimum, assessments at baseline and at 12 months (± 8 weeks). Also, patients without a confirmed diagnosis of NPC, if any, were to be excluded from the set. The CAS was to be used for selected efficacy analyses. Patients who received the wrong treatment in error were to be excluded from these efficacy analyses.

Safety Set

The safety set was defined as all patients who have received at least one dose of study drug. The safety set was planned to be used for all safety analyses. Since all patients less than 12 years of age were to receive a dose of arimoclomol for PK assessment (even if randomised to placebo), the safety analysis was planned to be presented by treatment period. Patients who used the escape route were to

be censored at the point where they start rescue medication. All AEs occurring after a dose of rescue medication was taken were planned to be presented separately.

Statistical analysis methods

In general, data was planned to be summarised by treatment group.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard error [SE], SD, median, minimum and maximum) were to be presented when relevant. Least Squares mean (LS mean), SE and 95% confidence interval (CI) were to be presented in the statistical analysis outputs as appropriate. In summary tables of categorical variables, the number of non-missing observations by category was to be presented with percentages. Unless otherwise specified, the denominator for each percentage was planned to be the number of non-missing observations within the column. Patient characteristics at baseline as well as characteristics of the disease were planned to be analysed using standard descriptive statistical methods.

All hypothesis testing was planned to be carried out at the 5% (2-sided) significance level. All statistical analysis were planned to be performed using SAS 9.3 or higher.

Primary Efficacy Analysis

Treatment comparisons were supposed to be arimoclomol vs placebo up to 12 months only, since after this timepoint all patients were supposed to be taking arimoclomol. The main analysis set for the efficacy analyses was to be carried out in the FAS, and all efficacy analysis were to be repeated for the PP Set and CAS.

A general linear mixed model for repeated measurements (MMRM) was planned be used to analyse the primary endpoint, defined as the change from baseline to 12 months in the 5 domain NPCCSS. The 5 domain NPCCSS score was derived as the sum of scores from the ambulation, speech, swallow, fine motor skills and cognition domains. The estimated treatment effect was to be presented with a 95% CI and a p-value to test the null hypothesis that the effect of arimoclomol and placebo is the same.

For sensitivity purposes, the primary analysis was planned to be repeated using 3 different imputation methods to estimate missing 5 domain NPCCSS scores at 12 months. Subgroup analyses were planned to be performed on the primary endpoint. Point estimates of treatment differences with 95% CIs and proportions of treatment difference with 95% CIs were to be presented for each subgroup where applicable.

The subgroups to be analysed were:

- use or not of miglustat at randomisation
- genotype
- age at diagnosis of first neurological symptom. Categories were:
    - o pre/peri-natal (onset at age < 3 months)
    - o early-infantile (at age 3 months to < 2 years)
    - o late-infantile (at age 2 to < 6 years)
    - o juvenile (at age 6–15 years)
    - o adolescent/adult (at age >15 years)
- age at entry to the study either < 12 years or >= 12 years
- age at entry to the study either < 4 years or >=4 years

• disease severity defined as the 5 domain NPCCSS score at baseline divided into 3 severity groups <4, 4-22 and >22

• disease severity defined as the full scale NPCCSS apart from hearing domains score at baseline divided into tertiles; 0 - ≤18, 19 - ≤36, 37 - ≤54)

• change in full scale NPCCSS score apart from hearing domains at 3 and 6 months (from baseline) were to be analysed for patients with late infantile phenotype (age at the start of neurological symptoms: at age 2 to < 6 years)

Forest plots were planned to be presented displaying the point estimates of treatment differences with 95% CIs or proportions of treatment difference with 95% CIs, by the subgroup categories mentioned above.

Secondary Efficacy Analysis

Key secondary efficacy evaluation

Responder analyses were to be performed using the following definitions:

- Patient's CGI-I score remains stable or shows improvement at 12 months (note that for the FDA submission, this endpoint was considered a co-primary endpoint),

- Patient's 5 domain NPCCSS score remains stable or improves at 12 months compared to baseline

These responder key secondary endpoints were planned to be analysed using two-tailed chi-squared tests on the FAS and were to be repeated for the PP set and the CAS. A patient who discontinued before 12 months was to be considered a nonresponder.

Time to worsening (months), as defined by reaching the MCID on patient's 5 domain NPCCSS was derived as the difference between date of first dose and the date that patient's 5 domain NPCCSS reaches the MCID. Kaplan-Meier plots for time to worsening (months) were to be produced for each treatment group on the FAS and were to be repeated for the PP set and the CAS. The median time to worsening (months) for each treatment and the corresponding 2-sided 95% CI were planned to be presented along with a two-sided logrank test, stratified for use of miglustat, to compare time to worsening between the two treatments.

The proportions of patients who have shown worsening by 6 months and by 12 months: Worsening was defined as patients that have reached the MCID on their 5 domain NPCCSS. This was planned to be analysed using two-tailed chi-squared tests on the FAS and will be repeated for the PP set and the CAS. A patient who discontinues before 6 months (or 12 months, as appropriate) was to be considered a patient who has worsened.

Full scale NPCCSS apart from hearing domains change from baseline to 12 months: The change in full scale NPCCSS apart from hearing domains from baseline to 12 months was to be analysed using an ANCOVA model including baseline full scale NPCCSS apart from hearing domains score, use of miglustat and randomised treatment as covariates on the FAS and was to be repeated for the PP set and the CAS.

Other secondary efficacy endpoints

The SAP contained all details regarding the (comparative) statistical analyses for the predefined variables: NPCCSS Score, NPC-CDB Score, EQ-5D-Y, SARA Score, 9HPT Time, CGI-I, CGI-S. Data was planned to be analysed and summarised by appropriate descriptive measures. More elaborate inferential statistical methods were planned to be applied for NPCCSS Score and EQ-5D-Y to the describe the potential treatment effect.

Subgroup analyses similar as planned for the primary efficacy endpoint were also planned for the set of secondary endpoints.

Exploratory Efficacy Analysis

Various analyses for rate of disease progression were foreseen as additional exploratory investigations, also including annual progression information for those patients who rolled over from CT-ORZYNPC-001 study.

Biological markers were planned be assessed in blood and skin punch biopsy samples at baseline, 6 and 12 months. Absolute values and changes from baseline in each of the biomarkers were to be derived and summarised using descriptive statistics on the FAS.

In order to perform an exploratory exposure-response analysis, sampling for POP PK was planned to be performed in all patients at 3, 6, 9 and 12 months. Results from PK sampling were to be summarised using descriptive statistics on the FAS, by dose group.

Safety analysis

According to the SAP, standard descriptive methods were planned for the statistical evaluation of Adverse-Events data. Laboratory parameters (mean and change from baseline) were planned to be summarised at each visit using descriptive statistics. Shift tables were to be produced for all laboratory parameters showing whether observed values are normal, low or high at baseline and each patient's final visit. Incidence of abnormal laboratory values and alert values by visit and overall were planned to be summarised by laboratory parameter. As regards vital signs, mean and change from baseline in blood pressure, pulse rate, respiratory rate and temperature were planned to be summarised for each visit using descriptive statistics.

Results

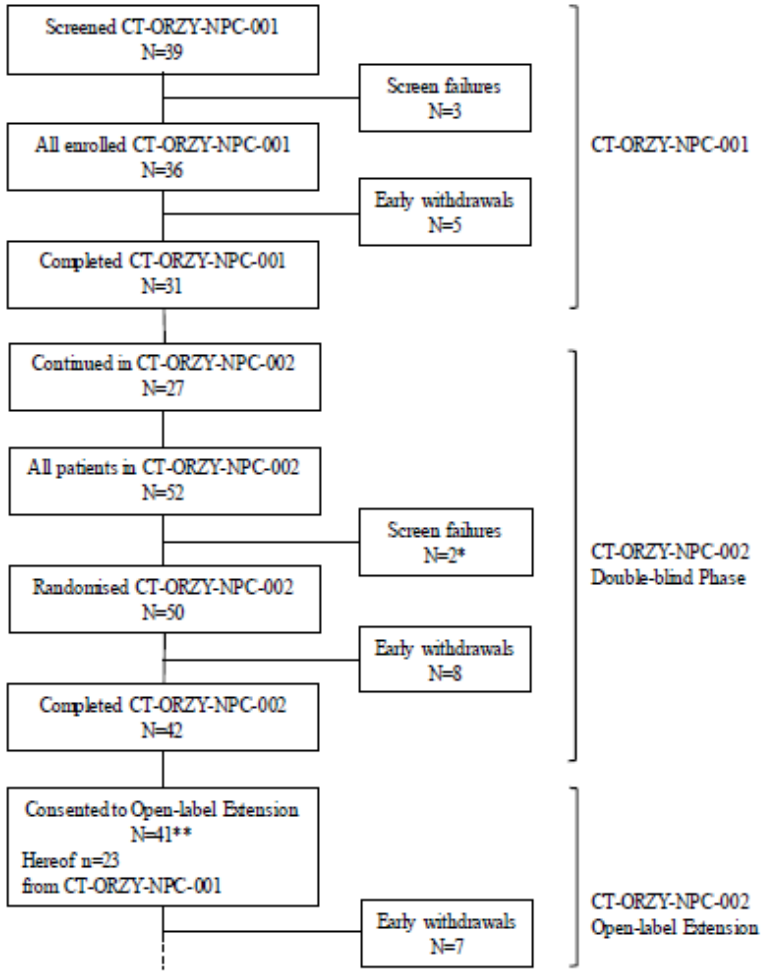
Participant flow

The flow of patients from the observational trial CT-ORZY-NPC-001, continuing into the double-blind treatment phase of CT-ORZY-NPC-002 and further into the open-label extension phase of CT-ORZY-NPC-002 is illustrated in Figures 3-1 and 3-2.

In total, 36 patients were enrolled in the observational trial (no treatment administered) CT-ORZY-NPC-001 of which 27 patients continued into the double-blind treatment phase of trial CT-ORZY-NPC-002.

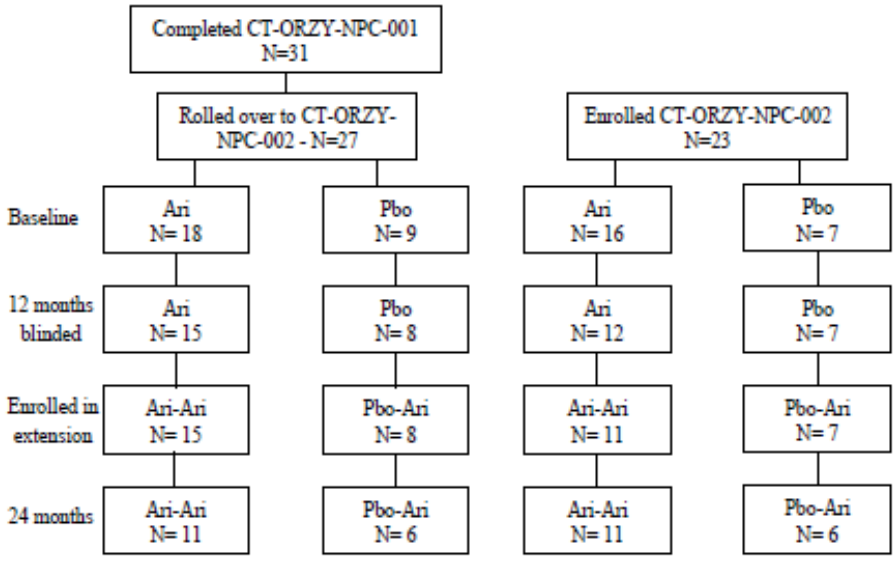
The double-blind treatment phase of CT-ORZY-NPC-002 included a total of 50 randomised patients, where 42 patients completed the treatment phase and 41 of these patients continued into the open-label extension phase.

Figure 3-1 **Patient Disposition Across Trials CT-ORZY-NPC-001 and CT-ORZY-NPC-002**



*One patient received single-dose PK

Figure 3-2 **Patient Disposition Across Trials**



Baseline data

CT-ORZY-NPC-002 Double-blind Phase

Demographic, Baseline and Disease Characteristics:

Table 10-4r Demographics, Baseline and Disease Characteristics (FAS)

		Arimoclomol (n=34)	Placebo (n=16)	Total (n=50)
Age (years)	Mean (SD)	11.5 (5.4)	10.2 (4.1)	11.1 (5.0)
Sex	Male	17 (50.0%)	7 (43.8%)	24 (48.0%)
	Female	17 (50.0%)	9 (56.3%)	26 (52.0%)
Race	White	32 (94.1%)	13 (81.3%)	45 (90.0%)
	Asian	1 (2.9%)	1 (6.3%)	2 (4.0%)
	Native Hawaiian or Other Pacific Islander	-	1 (6.3%)	1 (2.0%)
	Other	1 (2.9%)	1 (6.3%)	2 (4.0%)
BMI (kg/m^2)	Mean (SD)	18.72 (4.15)	19.46 (3.33)	18.95 (3.89)
Time since first NPC symptom	Mean (SD)	7.61 (4.54)	8.07 (3.75)	7.76 (4.27)
Age at diagnosis of first neurological symptom (years)	Mean (SD)	5.05 (3.43)	5.22 (3.87)	5.10 (3.54)
Time since NPC diagnosis (years)	Mean (SD)	5.59 (4.36)	5.11 (4.14)	5.43 (4.25)
5-Domain NPCCSS score	Mean (SD)	12.1 (6.9)	9.4 (6.4)	11.2 (6.8) -
Full scale NPCCSS except hearing domains	Mean (SD)	21.2 ~~21.1~~ (11.5)	17.2 (11.3)	19.9 (11.4) -
Currently treated with miglustat	Yes	26 (76.5%)	13 (81.3%)	39 (78.0%)
	No	8 (23.5%)	3 (18.8%)	11 (22.0%)

Source: modified from [Tables 14.1.3.1, 14.1.5.1, 14.2.1.1r, and 14.2.2.5.1r]

Two subgroups were defined post hoc as they were considered interesting according to the patients' mutations and expected outcome. This included patients without double functional null mutations and patients with at least one known ER missense mutations. Three (3) patients had double functional null mutations, all randomised to the arimoclomol group (Table 2-12), and 11 patients in the arimoclomol group and 4 patients in the placebo group had ER mutations.

Table 2-12 Patient Genotype by Mutation Type

Patient genotype	Arimoclomol (n=34)	Placebo (n=16)	Total (n=50)
Double functional null	3 (8.82%)	0 (0%)	3 (6%)
Double missense	16 (47.06%)	11 (68.75%)	27 (54%)
Missense / functional null	15 (44.18%)	5 (31.25%)	20 (40%)

Source: [5.3.5.4 CT-ORZY-NPC-002-016 genotype report, Table 6]

The n values denote the number of patients in each group

CT-ORZY-NPC-002 Open-label Phase

Demographic and Baseline Characteristics:

Table 10-3 Demographics and Baseline Characteristics

		Arimoclomol-arimoclomol (n=26)	Placebo-arimoclomol (n=15)	Total (n=41)
Age (years)	Mean (SD)	12.70 (5.1)	11.70 (4.3)	12.30 (4.8)
Gender	Male	13 (50.0%)	7 (46.7%)	20 (48.8%)
	Female	13 (50.0%)	8 (53.3%)	21 (51.2%)
Race	White	24 (92.3%)	12 (80.0%)	36 (87.8%)
	Asian	1 (3.8%)	1 (6.7%)	2 (4.9%)
	Native Hawaiian or Other Pacific Islander	-	1 (6.7%)	1 (2.4%)
	Other	1 (3.8%)	1 (6.7%)	2 (4.9%)
BMI (kg/m^2)	Mean (SD)	20.10 (4.3)	20.60 (4.2)	20.30 (4.2)

The denominator for each percentage is the number of non-missing observations within the column.

Abbreviations: BMI = body mass index; SD = standard deviation.

Source: Modified from [Table 14.1.3.1e].

Disease Characteristics:

Table 10-4 Disease Characteristics at Baseline 2

		Arimoclomol-arimoclomol (n=26)	Placebo-arimoclomol (n=15)	Total (N=41)
NPC1 diagnosis	n (%)	26 (100%)	15 (100%)	41 (100%)
Time since first NPC symptom (years)	Mean (SD)	7.92 (4.45)	8.37 (3.68)	8.08 (4.14)
Currently treated with miglustat				
Yes		21 (80.8%)	12 (80.0%)	33 (80.5%)
No		5 (19.2%)	3 (20.0%)	8 (19.5%)
NPCCSS total score	Mean (SD)	22.3 (12.8)	19.9 (13.3)	21.4 (12.8)
5-domain NPCCSS total score	Mean (SD)	12.7 (7.9)	11.5 (7.7)	12.3 (7.8)
5-domain NPCCSS; individual domain scores				
Ambulation score	Mean (SD)	2.8 (1.7)	2.5 (1.8)	2.7 (1.7)
Speech score	Mean (SD)	2.0 (1.6)	1.9 (1.5)	2.0 (1.6)
Swallow score	Mean (SD)	2.1 (2.1)	2.0 (2.0)	2.0 (2.0)
Fine motor skills score	Mean (SD)	2.8 (1.9)	2.5 (1.7)	2.7 (1.8)
Cognition score	Mean (SD)	3.0 (1.4)	2.6 (1.5)	2.9 (1.4)

The denominator for each percentage is the number of non-missing observations within the column.

Time since first NPC symptom(s) (years) - calculated using the date of initial symptom and the date of Visit 1 (Baseline 1).

Time since NPC diagnosis (years) - calculated using date of NPC diagnosis on NPC-cdb patient history questionnaire and date of Visit 1.

Abbreviations: NPC = Niemann-Pick disease type C; NPC-cdb = NPC clinical database; NPCCSS = NPC clinical severity scale; SD = standard deviation.

Numbers analysed

CT-ORZY-NPC-002 Double-blind Phase

All decisions on inclusion and exclusion of patients from analysis sets were made prior to unblinding. The allocation of patients to the analysis sets is summarised in Table 10-2.

Table 10-2 Patient Disposition

	Arimoclomol	Placebo	Total
Full Analysis Set	34	16	50
Per Protocol Set	27	15	42
Completers Analysis Set	25	15	40
Safety Set	34	16	51*

CT-ORZY-NPC-002 Open-label Phase

The extension set was used for data analysis, which included all patients who received at least 1 dose of the IMP in the extension phase. The allocation of patients to this analysis set is summarised in Table 10-2.

Table 10-2 Analysis Set

	Arimoclomol-arimoclomol (N=34)	Placebo-arimoclomol (N=16)	Total (N=50)
Completed blinded phase	27	15	42
Extension set	26	15	41
Available for PK sampling	6 (23.1%)	7 (46.7%)	13 (31.7%)

The denominator for each percentage is the number of patients in the extension set.

Abbreviations: PK = pharmacokinetics

Source: Modified from [Table 14.1.2e]

Outcomes and estimation

Primary Efficacy Endpoint

Change in NPC disease severity based on the 5-domain NPCCSS scores from Baseline to 12 months

CT-ORZY-NPC-002 Double-blind Phase

In the analysis of the primary endpoint using the FAS there was a borderline treatment effect in favour of arimoclomol over placebo of -1.40 (p=0.0456) (Table 11-1r).

Table 11-1r Analysis of change from baseline in 5-domain NPCCSS score at 12 months

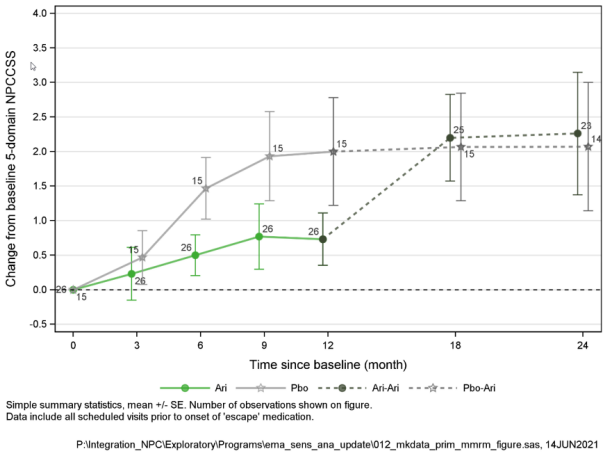
	Arimoclomol (N=34)	Placebo (N=16)	Estimated treatment effect: Arimoclomol vs Placebo (95% CI)	p-value
Baseline				
N	34	16		
Mean	12.1	9.4		
SD	6.9	6.4		
12 months				
N	27	15		
Mean	13.0	11.5		
SD	8.0	7.7		
Change from baseline to 12 months				
N	27	15		
Mean	0.7	2.0		
SD	1.9	3.0		
General Linear Mixed Model for Repeated Measures				
Treatment Effect			-1.40 (-2.76, -0.03)	0.0456
Miglustat Level				<0.0001
Baseline Score				0.0395

Full analysis set. General linear mixed model for repeated measures fitted with treatment, miglustat level and visit as fixed effects including treatment-by-visit interaction and baseline score as covariate.
Source: modified from Table 14.2.1.1r

In the primary analysis, there was a mean change (disease progression) in the arimoclomol group of 0.76 (95% CI: -0.05, 1.56) and in the placebo group of 2.15 (95% CI: 1.05, 3.25). This represents a treatment effect in favour of arimoclomol over placebo of -1.40 (95% CI: -2.76, -0.03; p=0.0456).

The estimated change in 5-domain NPCCSS from Baseline to 12 months is presented in Figure 2.17r.

Figure 2-17r **Change from Baseline in 5-domain NPCCSS – Double-blind Phase and Open-label Extension Phase – Extension Set**



Source: [M5.3.5.3 Figure Cr]

CT-ORZY-NPC-002 Open-Label Phase

For the open-label phase of study CT-ORZY-NPC-002, the mean 5-domain NPCCSS score by planned visit from Baseline 1 is visualised in Figure 2-16 (dotted grey line) and change from Baseline 1 in 5-domain NPCCSS is presented in Figure 2-17 (dotted grey line).

Analysis of Other Secondary Endpoints

CT-ORZY-NPC-002 Double-blind Phase

Change in Individual domains of the 5-domain NPCCSS

Table 2-16r Mean Baseline Scores for the Individual Domains of the 5-domain NPCCSS and Change from Baseline at 12 Months

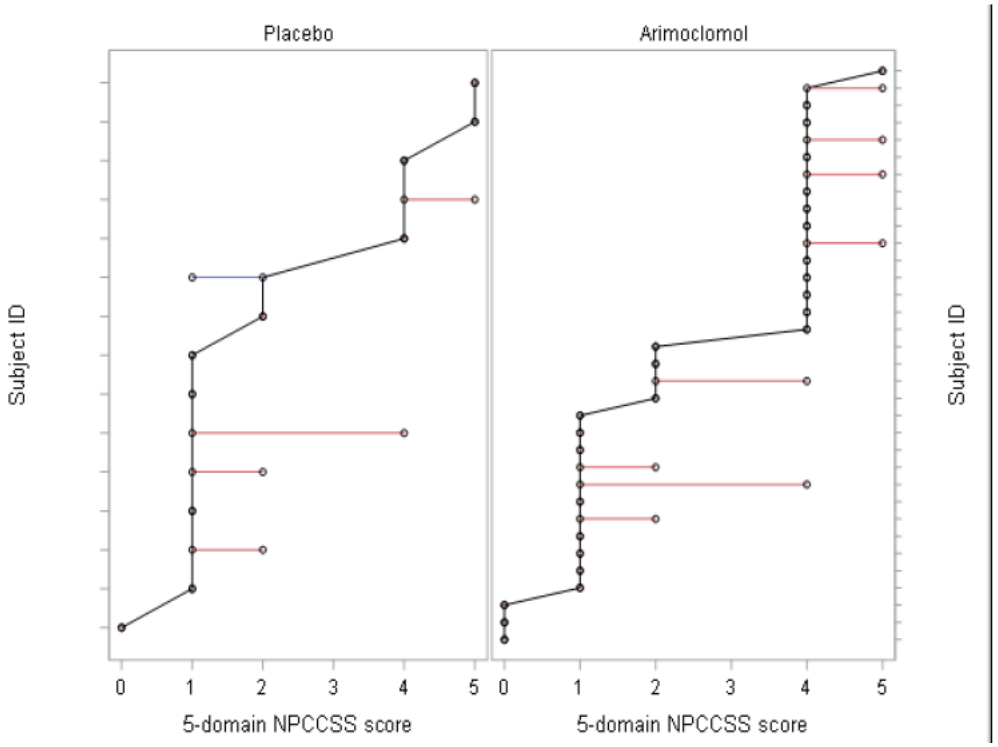
		Arimoclomol (N=34)	Placebo (N=16)
Ambulation	Baseline; mean (SD)	2.5 (1.6)	2.2 (1.6)
	Change at 12 months; mean (SD)	0.3 (0.5)	0.3 (0.9)
Speech	Baseline; mean (SD)	2.2 ~~2.1~~ (1.6)	1.6 (1.2)
	Change at 12 months; mean (SD)	-0.2 ~~-0.1~~ (1.0)	0.3 (0.8)
Swallow	Baseline; mean (SD)	1.9 (1.7)	1.3 (1.7)
	Change at 12 months; mean (SD)	0.1 (1.1)	0.6 (1.0)
Fine motor skills	Baseline; mean (SD)	2.8 (1.8)	1.9 (1.8)
	Change at 12 months; mean (SD)	0.2 (0.8)	0.6 (1.3)
Cognition	Baseline; mean (SD)	2.8 (1.3)	2.5 (1.5)
	Change at 12 months; mean (SD)	0.3 (0.6)	0.1 (0.6)

Source: [CT-ORZY-NPC-002 DB, Table 14.2.2.8.1r]

Patient level plots for each of the 5 domains are presented in Figure 2-7 to Figure 2-11 (for baseline to last available data, FAS).

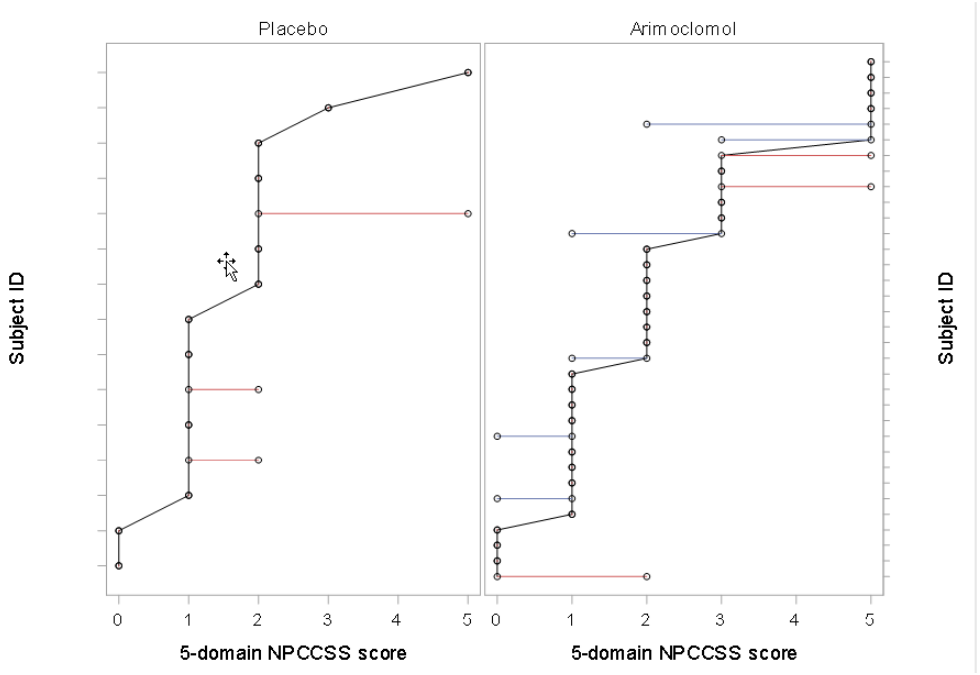
For the ambulation domain, the mean baseline score was higher in the arimoclomol group compared to the placebo group (2.5 versus 2.2). The proportion of patients who worsened from baseline to 12 months (had a higher score) were comparable between the treatment groups, one patient in the placebo group improved (had a decreased score) (Figure 2-7). The mean change from baseline to 12 months was 0.3 in both treatment groups.

Figure 2-7 **Patient Level Plot for Ambulation – Baseline to Last Available Data – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



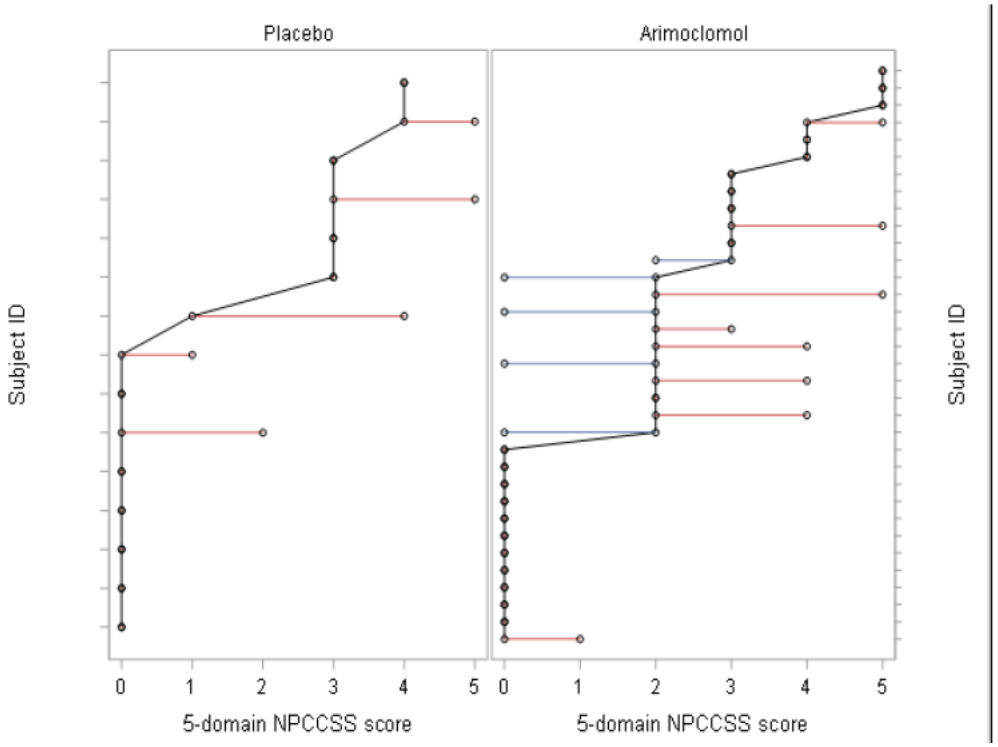
For the speech domain, the mean baseline score was higher in the arimoclomol group compared to the placebo group (2.2 versus 1.6). The proportion of patients who worsened (had an increased score) from baseline to 12 months was lower in the arimoclomol group and 5 patients in the arimoclomol group improved (had a decreased score); none of the patients in the placebo group improved (Figure 2-8r). The mean change from baseline to 12 months was -0.2 (improvement) in the arimoclomol group and 0.3 (worsening) in the placebo group.

Figure 2-8r **Patient Level Plot for Speech – Baseline to Last Available Data – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



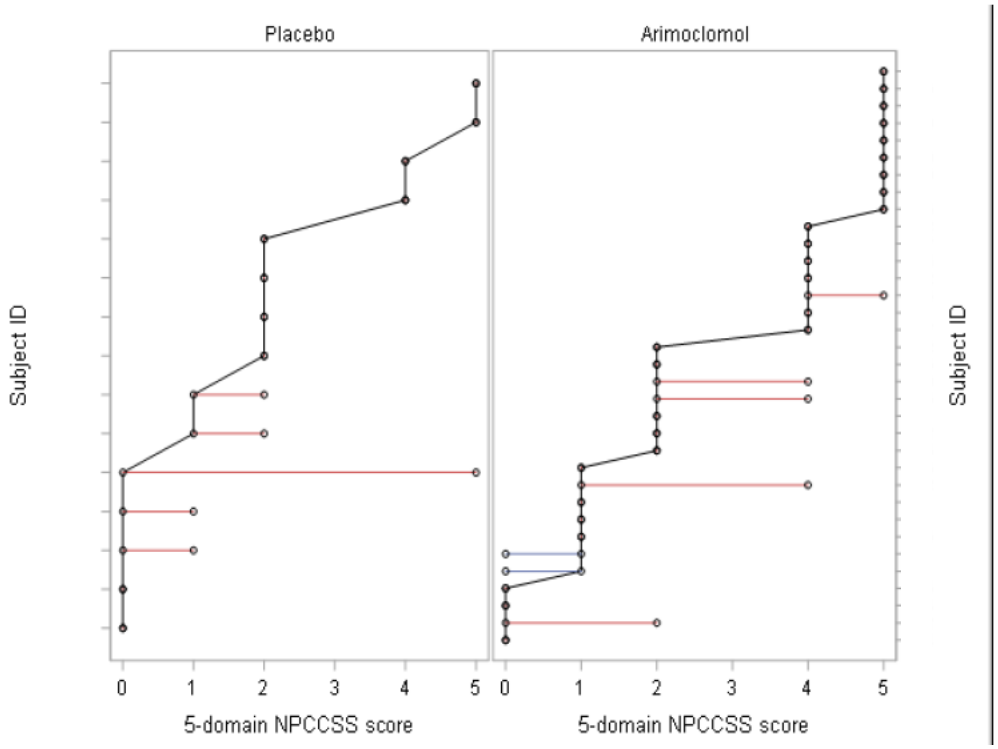
For the swallow domain, the mean baseline score was higher in the arimoclomol group compared to the placebo group (1.9 versus 1.3). The proportion of patients who worsened from baseline to 12 months (had a higher score) was lower in the arimoclomol group. Five patients in the arimoclomol group improved (had a decreased score) compared to none in the placebo group (Figure 2-9). The mean change from baseline to 12 months was 0.1 in the arimoclomol group and 0.6 in the placebo group, both reflecting a worsening.

Figure 2-9 **Patient Level Plot for Swallow – Baseline to Last Available Data – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



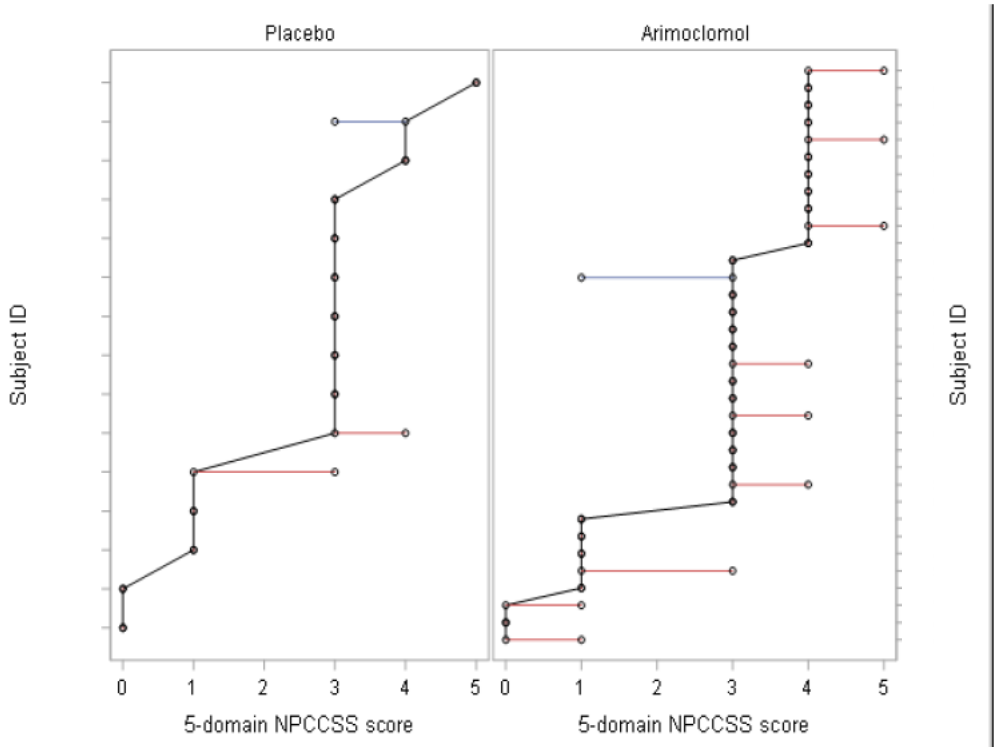
For the fine motor skill domain, the mean baseline score was higher in the arimoclomol group compared to the placebo group (2.8 versus 1.9). The proportion of patients who worsened from baseline to 12 months was lower in the arimoclomol group compared to the placebo group and two patients in the arimoclomol group improved (had a decreased score) (Figure 2-10). The mean change from baseline to 12 months was 0.2 in the arimoclomol group and 0.6 in the placebo group, both reflecting a worsening.

Figure 2-10 **Patient Level Plot for Fine Motor Skills – Baseline to Last Available Data – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



For the cognition domain, the mean baseline score was higher in the arimoclomol group compared to the placebo group (2.8 versus 2.5). The proportion of patients who worsened from baseline to 12 months was higher in the arimoclomol group compared to the placebo group and a lower proportion of patients improved in the arimoclomol group (i.e. one patient in each group) (Figure 2-11). The mean change from baseline to 12 months was 0.3 in the arimoclomol group and 0.1 in the placebo group, both reflecting a worsening.

Figure 2-11 **Patient Level Plot for Cognition – Baseline to Last Available Data – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



Change in Quality of Life (EQ 5D Y) at 6 and 12 months

Table 14.2.2.10.5.1 Analysis of EQ-5D-Y Using Pareto Principle (Full Analysis Set)

		Arimoclomol (N=34)	Placebo (N=16)	Total (N=50)	p-value
Change from baseline to 6 months	N	30	15	45	
	Better	5 (16.7%)	4 (26.7%)	9 (20.0%)	
	Worse	12 (40.0%)	7 (46.7%)	19 (42.2%)	
	Mixed	4 (13.3%)	1 (6.7%)	5 (11.1%)	
	Same	9 (30.0%)	3 (20.0%)	12 (26.7%)	
Chi-squared test	Better				0.6951
	Worse				0.7542
Change from baseline to 12 months	N	27	15	42	
	Better	7 (25.9%)	6 (40.0%)	13 (31.0%)	
	Worse	12 (44.4%)	3 (20.0%)	15 (35.7%)	
	Mixed	4 (14.8%)	0	4 (9.5%)	
	Same	4 (14.8%)	6 (40.0%)	10 (23.8%)	
Chi-squared test	Better				0.4880
	Worse				0.1804

Better = Better on at least one dimension and no worse on any other dimension.
Worse = Worse on at least one dimension, and no better on any other dimension.
Mixed = Better on one dimension, but worse on another.
Same = No change in any dimension.

Table 14.2.2.10.2.1 Analysis of Change from Baseline in Quality of Life (EQ-5D-Y) VAS Scores (Full Analysis Set)

	Arimoclomol (N=34)	Placebo (N=16)	Total (N=50)	p-value
Change from baseline to 6 months				
Mann-Whitney test: Median (95% CI)	4.50 (-10.00, 10.00)	0.00 (-5.00, 10.00)	0.00 (-5.00, 10.00)	0.9710
Change from baseline to 12 months				
Mann-Whitney test: Median (95% CI)	0.00 (-7.00, 5.00)	0.00 (-5.00, 10.00)	0.00 (-5.00, 5.00)	0.6625

Key Secondary Efficacy Endpoints

CT-ORZY-NPC-002 Double-blind Phase

Responder analysis of patient's CGI-I score at 12 months (the endpoint was considered co-primary by the FDA)

Table 11-3 Analysis of Responders: CGI-I

	Arimoclomol (N=34)	Placebo (N=16)	Total (N=50)	p-value
Responder at 12 months				
N	34	16	50	
Yes	20 (58.8%)	9 (56.3%)	29 (58.0%)	
No	14 (41.2%)	7 (43.8%)	21 (42.0%)	
Chi-squared test				1.0000

Full analysis set. Patients who discontinued before 12 months have been imputed as non-responders (6 on arimoclomol, 1 on placebo).
Source: [Table 14.2.2.1.1]

Responder analysis of patient's NPCCSS score at 12 months

Table 11-4 Analysis of Responders: 5-Domain NPCCSS

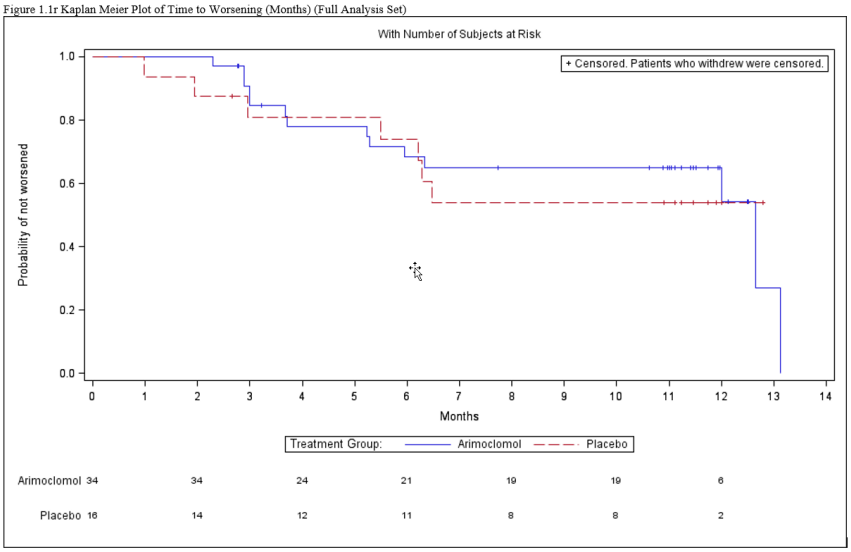
	Arimoclomol (N=34)	Placebo (N=16)	Total (N=50)	p-value
Responder at 12 months				
N	34	16	50	
Yes	17 (50.0%)	6 (37.5%)	23 (46.0%)	
No	17 (50.0%)	10 (62.5%)	27 (54.0%)	
Chi-squared test				0.5456

Full analysis set. Patients who discontinued before 12 months have been imputed as non-responders (6 on arimoclomol, 1 on placebo).
Source: [Table 14.2.2.2.1]

Time to Worsening

In the time to worsening analysis (defined as the time until the patient reached the predefined MCID of 2 points compared to baseline on the 5-domain NPCCSS), the 25th percentile Kaplan-Meier estimate was 5.2 months (95% CI: 2.9; 12.0) for arimoclomol and 5.5 months (95% CI: 1.0; 6.5) for placebo (p=0.8021) using the FAS.

Figure 1.1r Kaplan Meier Plot of Time to Worsening (Months) (Full Analysis Set)



Proportion of Patients Worsening

Table 11-5r Analysis of Worsening at 6 and 12 Months

		Arimoclomol (N=34)	Placebo (N=16)	p-value
Worsening at	Yes	12 (35.3%)	8 (50.0%)	
	No	22 (64.7%)	8 (50.0%)	
	Fisher's exact test			0.3662
Worsening at	Yes	15 (44.1%)	7 (43.8%)	
	No	19 (55.9%)	9 (56.3%)	
	Fisher's exact test			1.0000

Full analysis set
Worsening is defined as;
1) Patients that have reached the Preferred MCID on their 5-domain NPCCSS.
2) Discontinuation before 6 months or 12 months respectively will be considered as worsened.
3) Missing scores at 6 months or 12 months respectively will also be considered as worsened.
Source: Table 14.2.2.4.1r

Change in Full Scale NPCCSS (Apart from Hearing Domains) Score at 6 and 12 Months

Table 11-6r Analysis of Change from Baseline in Full Scale NPCCSS (Apart from Hearing Domains) Score at 6 and 12 months

		Arimoclomol (N=34)	Placebo (N=16)	Arimoclomol vs Placebo: LS Mean Difference (95% CI) and p value
Change from baseline to 6 months				
ANCOVA model	Treatment: LS Mean (95% CI)	0.53 (-0.85, 1.90)	2.22 (0.33, 4.10)	-1.69 (-4.04, 0.66) p=0.1546
	Baseline full scale NPCCSS apart from hearing domains score			p=0.5209
Change from baseline to 12 months				
ANCOVA model	Treatment: LS Mean (95% CI)	1.20 (-0.40, 2.79)	2.81 (0.75, 4.87)	-1.61 (-4.24, 1.01) p=0.2199
	Baseline full scale NPCCSS apart from hearing domains score			p=0.5275

Full analysis set
ANCOVA model is fitted with treatment, baseline full scale NPCCSS apart from hearing domains score and use of miglustat as covariates.
Source: modified from Tables [14.2.2.5.1r and 14.2.2.7.2.1r]

Exploratory Biomarker Endpoints

CT-ORZY-NPC-002 Double-blind Phase:

The key biomarkers measured are summarised in Table 2-17.

Table 2-17 Summary of Biomarkers – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)

		Arimoclomol (N=34)	Placebo (N=16)
Hsp70 in PBMC (pg/mL)			
Baseline	N	29	9
	Mean (SD)	1356.271 (464.075)	1859.176 (815.182)
12 months	N	13	4
	Mean (SD)	2772.533 (1593.010)	2526.055 (1355.242)
Change from baseline to 12 months	N	11	4
	Mean (SD)	1778.984 (1835.558)	1022.393 (1984.974)
Un-esterified cholesterol in PBMC (ng/mg protein)			
Baseline	N	33	11
	Mean (SD)	78744.2 (66602.0)	56109.7 (19862.8)
12 months	N	24	14
	Mean (SD)	110740.6 (92538.2)	113875.3 (82338.6)
Change from baseline to 12 months	N	23	10
	Mean (SD)	29854.9 (52653.2)	71725.6 (87883.1)
Cholestane-triol (Oxysterols) in serum (ng/mL)			
Baseline	N	34	15
	Mean (SD)	84.411 (31.002)	84.664 (23.964)
12 months	N	27	15
	Mean (SD)	78.613 (32.428)	85.294 (26.222)
Change from baseline to 12 months	N	27	14
	Mean (SD)	-7.450 (13.121)	-0.894 (13.325)

Full analysis set
Source: [CT-ORZY-NPC-002 DB, Table 11-12]

CT-ORZY-NPC-002 Open-label Phase:

Table 2-22 Summary of Biomarkers – Open-label Extension Phase CT-ORZY-NPC-002 (Extension Set)

	Arimoclomol-Arimoclomol	Placebo-Arimoclomol
HSP70 in PBMC (pg/mL)		
Baseline 1		
N	23	8
Mean (SD)	1330.4 (456.81)	1935.5 (836.35)
Baseline 2		
N	25	9
Mean (SD)	2313.2 (1316.6)	2287.9 (1046.6)
24 months		
N	17	10
Mean (SD)	2268.9 (1096.5)	2317.8 (766.02)
Change from Baseline 1 to 24 months		
N	15	4
Mean (SD)	1040.0 (1178.8)	903.24 (839.29)
Change from Baseline 2 to 24 months		
N	17	5
Mean (SD)	-222.6 (1817.5)	-355.6 (692.52)
Un-esterified cholesterol in PBMC (ng/mg protein)		
Baseline 1		
N	26	10
Mean (SD)	80745 (74775)	55111 (20644)
Baseline 2		
N	26	14
Mean (SD)	102444 (89304)	113875 (82339)
24 months		
N	17	7
Mean (SD)	45706 (19107)	29629 (11642))
Change from Baseline 1 to 24 months		
N	17	4
Mean (SD)	-43323 (93247)	-24965 (19219)
Change from Baseline 2 to 24 months		
N	17	6
Mean (SD)	-71067 (109675)	-50960 (26099)

As before

	Arimoclomol-Arimoclomol	Placebo-Arimoclomol
Cholestane-triol (Oxysterols) in serum (ng/mL)		
Baseline 1		
N	26	14
Mean (SD)	83.80 (34.00)	85.26 (24.75)
Baseline 2		
N	26	15
Mean (SD)	75.95 (33.10)	85.29 (26.22)
24 months		
N	22	13
Mean (SD)	75.07 (28.80)	82.38 (31.43)
Change from Baseline 1 to 24 months		
N	22	12
Mean (SD)	-6.41 (12.71)	-4.75 (13.14)
Change from Baseline 2 to 24 months		
N	22	13
Mean (SD)	-0.48 (11.70)	-1.82 (8.84)

Baseline 1= the baseline in the double-blind treatment phase; Baseline 2= the baseline in the open-label extension phase
Source: [CT ORZY-NPC-002 OL Interim, Tables 14.2.3.1e, 14.2.3.1e.2, and 14.2.3.2e]

Ancillary analyses

SUBGROUP ANALYSIS

CT-ORZY-NPC-002 Double-blind Phase

In line with the sensitivity analysis, age at trial entry and age at first neurological symptom did not seem to have an impact on the overall treatment effect of arimoclomol but there was a borderline treatment effect in patients above 4 years of age at trial entry (-1.80, 95% CI: -3.24; -0.35) and above 12 years of age (-3.18, 95% CI: -6.16; -0.20) (see Table 11-2r). A nominal treatment effect in favour of arimoclomol was also seen in patients with full NPCCSS (except hearing domain) <=18 at baseline in disease severity B (milder disease, range is 0 – 51) with a treatment effect -0.93 (95% CI: -1.77; -0.09).

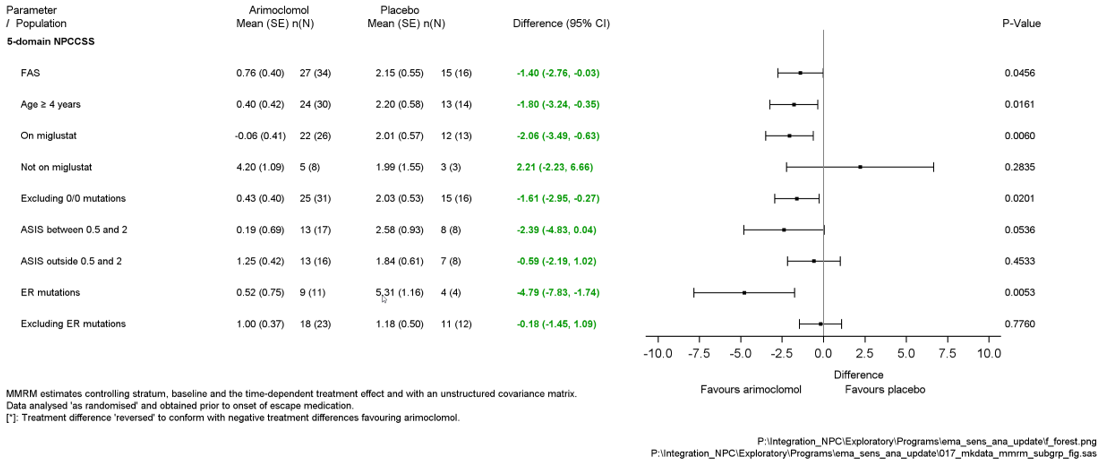
Table 11-2r Subgroup analysis of change in 5-domain NPCCSS Score from baseline to 12 months (Full Analysis Set)

	Arimoclomol (N=34)	Placebo (N=16)	Arimoclomol vs Placebo: Difference in LS Means (95% CI)
Analysis of change in 5 Domain NPCCSS Score from baseline to 12 months			
Patients per subgroup			
Use of miglustat	22	12	-2.06 (-3.49, -0.63)
No use of miglustat	5	3	2.21 (-2.14, 6.57)
Age at first neurological symptom: <3 months	1	0	
Age at first neurological symptom: 3 months to <2 years	5	3	-1.52 (-4.18, 1.14)
Age at first neurological symptom: 2 to <6 years	13	6	-1.23 (-2.69, 0.23)
Age at first neurological symptom: 6-15 years	8	6	-1.50 (-5.68, 2.69)
Age at first neurological symptom: >15 years	0	0	
Age at entry to study: < 12 years	12	10	-1.13 (-2.44, 0.19)
Age at entry to study: >= 12 years	15	5	-3.18 (-6.16, -0.20)
Age at entry to study: < 4 years	3	2	
Age at entry to study: >= 4 years	24	13	-1.80 (-3.24, -0.35)
Disease severity A: < 4	4	3	
Disease severity A: 4-22	21	11	-1.54 (-3.34, 0.26)
Disease severity A: > 22	2	1	
Disease severity B: 0 - <=18	11	10	-0.93 (-1.77, -0.09)
Disease severity B: 19 - <=36	12	4	-1.93 (-5.96, 2.10)
Disease severity B: 37 - <=54	3	1	

The Arimoclomol/Placebo column indicates the number of patients with data at Visit 6.
Disease Severity A defined using the 5 domain NPCCSS score at baseline. Disease Severity B defined using the full scale NPCCSS apart from hearing domains score at baseline.
Negative values indicate a benefit for Arimoclomol over placebo. Positive values favour placebo.
Orphazyme/ARIMOCLOMOL/NPC_002/current - tab_NPCCSS5_ASG_DB_ongoing.sas/tab_NPCCSS5_ASG_11_2_DB.rtf/29jun2021

A total of 2 prespecified (age and miglustat) and 3 post hoc (ASIS, functional null, and ER positive genotype) subgroup analyses, where baseline disease characteristics were more comparable than in the overall trial population, strongly supported the primary endpoint by demonstrating greater and clinically meaningful treatment differences in favour of arimoclomol (Figure 4-2); most of these were statistically significant.

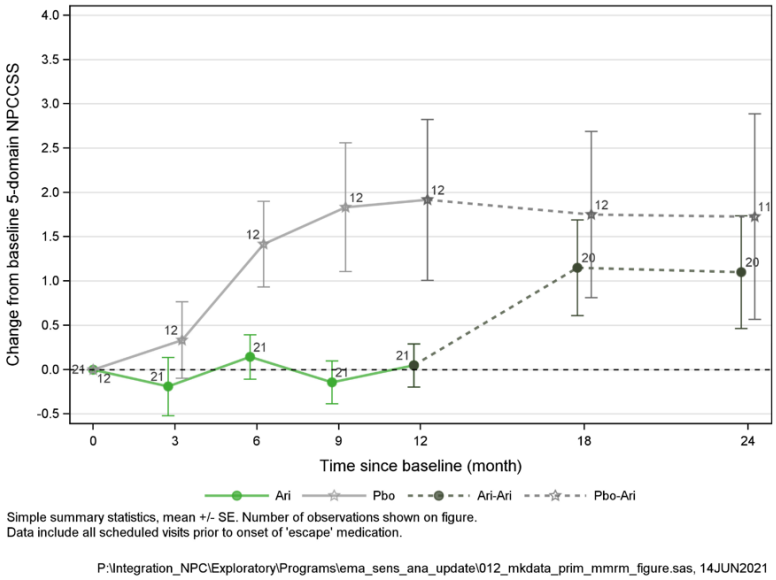
Figure 4-2r **Subgroup Analyses of Special Interest – Change from Baseline in 5-domain NPCCSS Score at 12 Months – Double-blind Treatment Phase CT-ORZY-NPC-002 (FAS)**



The number of patients in parenthesis are the number of patients with a 12-month assessment. No line for subgroups with very few patients.
Source: [M5.3.5.3 Efficacy Figure 1.5r, 1.6r and 1.7r]

The proportion of patients concomitantly treated with miglustat was comparable across treatment groups (76.5% in the arimoclomol group; 81.3% in the placebo group). This is in accordance with literature (Geberhiwot et al. 2018; Patterson et al. 2020). In the predefined subgroup of patients receiving miglustat, arimoclomol treatment as part of routine clinical care, arimoclomol treatment was associated with stabilisation of the clinical disease severity with a clinically meaningful difference on the 5-domain NPCCSS of -2.06 (95% CI [-3.49; -0.63]; p=0.0060) as compared to placebo at 12 months. This corresponds to a relative reduction of the disease progression of 103% (Figure 2-19r).

Figure 2-19r **Subgroup of Patients on Miglustat: Change from Baseline in 5-domain NPCCSS – CT-ORZY-NPC-002, Double-blind and Open-label Phase (Extension Set)**



Source: [M5.3.5.3 Figure Er]

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table. Summary of efficacy for trial CT-ORZY-NPC-002

Title: Arimoclomol Prospective Double-Blind, Randomised, Placebo-Controlled		
Study identifier	CT-ORZY-NPC-002	
Design	A randomised, placebo-controlled Phase 2/3 trial (CT-ORZY-NPC-002) consisting of a 12-month double-blind (DB) treatment phase evaluating efficacy and safety (completed) and a 12-month open-label (OL) extension phase evaluating long-term safety and efficacy for up to 48 months (ongoing). For the extension phase, 12 months interim data will be reported in this submission.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable 24 months (ongoing)

Hypothesis	Double blind phase: The model will be fitted with treatment, miglustat level and visit as fixed effects along with a treatment-by-visit interaction term. The estimated treatment effect will be taken from the treatment-by-visit interaction term at 12 months. The estimated treatment effect will be presented with a 95% CI and a p-value to test the null hypothesis that the effect of arimoclomol and placebo is the same (= superiority) Open label extended phase: To evaluate the long-term therapeutic response (clinical and biological assessments) of arimoclomol in patients with Niemann-Pick disease type C (NPC) at 18, 24, 30, and 36 months		
Treatments groups	Double blinded phase		Arimoclomol (dose based on body weight) plus standard of care. 12 months, 50 randomised, 34 treated, 27 completed Placebo plus standard of care. 12 months, 50 randomised, 16 treated, 15 completed
	Open-label (extended) phase		Arimoclomol (dose based on body weight) plus standard of care. 24 months (ongoing); all patients treated with arimoclomol
Endpoints and definitions	Primary endpoint	5-domain NPCCSS	Change in the NPC disease severity based on the 5-domain NPC Clinical Severity Scale (NPCCSS) scores (ambulation, speech, swallow, fine motor skills and cognition) from baseline (Visit 1) to 12 months (Visit 6) (double blind phase), and from Baseline 1 and 2, respectively, at 18, 24, 30, and 36 months (OL phase).
	Key Secondary endpoint	CGI-I	Responder analysis if Patient's Clinical Global Impression Scale of Improvement (CGI-I) score remains stable or shows improvement at 12 months (double blind), and remains stable or improves compared to Baseline 1 and 2 at 18, 24, 30, and 36 months (OL phase)
		Responder analysis if Patient's 5-domain NPCCSS score	Responder analysis if Patient's 5-domain NPCCSS score remains stable or improves at 12 months compared to baseline (double blind), and remains stable or improves compared to Baseline 1 and 2 at 18, 24, 30, and 36 months (OL phase)
		Time to worsening	Time to worsening (as defined by reaching the minimal clinically important difference (MCID) on patient's 5-domain NPCCSS).
		Proportion of patients worsening	Proportion of patients worsening (as defined by reaching the MCID on patient's 5-domain NPCCSS) at 6 and 12 months (double-blind) and at 18, 24, 30, and 36 months (OL phase)

		Change in full scale NPCCSS apart from hearing domains	Change in full scale NPCCSS apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 12 months (double-blind), and from Baseline 1 and 2, respectively, at 18, 24, 30, and 36 months (OL phase)
	Other Secondary Endpoints	Change in 5-domain NPCCSS at 6 months	Analysis of change from baseline in the 5-domain NPCCSS at 6 months
		Changes in each individual domain of the NPCCSS (excluding hearing domain)	Changes in each individual domain of the NPCCSS at 6 and 12 months (double-blind), and from Baseline 1 and 2, respectively, at 18, 24, 30, and 36 months (OL phase)
		Change in the NPC Clinical Database (NPC-CDB) score	Change in the NPC Clinical Database (NPC-CDB) score (modified "Stampfer Score") at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, and 36 months (OL phase)
		Change in Quality of Life (EQ 5D Y)	Change in Quality of Life (EQ 5D Y) at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, and 36 months (OL phase)
		Change in the Scale for Assessment and Rating of Ataxia (SARA) score	Change in the Scale for Assessment and Rating of Ataxia (SARA) score at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, and 36 months (OL phase)
		Change in the Nine-Hole Peg Test (9HPT)	Change in the Nine-Hole Peg Test (9HPT) at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, and 36 months (OL phase)
		Clinical Global Impression Scale of Severity (CGI-S)	Clinical Global Impression Scale of Severity (CGI-S) at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, 36 months (OL phase)
		Clinical Global Impression Scale - Improvement (CGI-I)	Clinical Global Impression Scale - Improvement (CGI-I) at 6 and 12 months (double-blind), and from Baseline 1 at 18, 24, 30, 36 months (OL phase)
	Exploratory Biomarker Endpoints	NPC1 protein function (cholesteryl esterification)	Changes at 6 and 12 months (placebo versus arimoclomol) and also at 18, 24, 30, and 36 months in OL phase
		Oxysterol (cholestane-3β,5α,6β-triol)	Changes at 6 and 12 months (placebo versus arimoclomol)

		Un-esterified cholesterol	Changes at 6 and 12 months (placebo versus arimoclomol) and also at 18, 24, 30, and 36 months in OL phase
		HSP70	Changes at 6 and 12 months (placebo versus arimoclomol) and also at 18, 24, 30, and 36 months in OL phase
		Glycosphingolipids	Changes at 6 and 12 months (placebo versus arimoclomol) and also at 18, 24, 30, and 36 months in OL phase
		Sphingoid bases	Changes at 6 and 12 months (placebo versus arimoclomol)
		Lyso-SM-509	Changes at 6 and 12 months (placebo versus arimoclomol)
Database lock	Double blind phase: - trial completion: 20 June 2018 - final database lock: 9 Dec 2019 Open label extended phase: - still ongoing; data from the first 12 months included in den interim study report		

Results and Analysis

Analysis description	**Primary Analysis: Double blind phase, 12 months**		
Analysis population and time point description	NPC patients randomised to arimoclomol vs placebo (2:1) together with standard of care treatment; comparing baseline (time point 0) to 12 months		
Descriptive statistics and estimate variability	Treatment group	Arimoclomol	Placebo
	Number of subject	34	16
	5 domain NPCCSS (change from baseline)	0.7	2.0
	standard deviation (SD)	1.9	3.0
Effect estimate per comparison	Primary endpoint: 5 domain NPCCSS	Comparison groups	Arimoclomol vs Placebo}
		difference between groups:	-1.40
		95% CI	-2.76, -0.03
		P-value	0.0456

Notes	In the analysis of the primary endpoint using the FAS there was a borderline treatment effect in favour of arimoclomol over placebo of -1.40 (p=0.0456)			
Analysis description	**Secondary analysis: double blind study phase**			
Analysis population and time point description	NPC patients randomised to arimoclomol vs placebo (2:1) together with standard of care treatment; comparing baseline (time point 0) to 12 months			
Effect estimate per comparison		Arimoclomol	Placebo	Arimoclomol vs Placebo
CGI-I	responder - yes:	58.8 %	56.3 %	-
	Nominal p-value	-	-	1.0000
Responder analysis if Patient's 5-domain NPCCSS score	responder - yes	50 %	37.5 %	-
	Nominal p-value	-	-	0.5456
Time to worsening	Mean change	5.2 months	5.5 months	-
	95% CI	2.9; 12.0	1.0; 6.5	-
	Nominal p-value	-	-	0.8021
Proportion of patients worsening	Worsening at 12 months - yes	44.1 %	43.8 %	-
	Nominal p-value	-	-	1.0000
Change in full scale NPCCSS apart from hearing domains	Mean change	1.20	2.81	-
	Mean difference			-1.61
	95% CI	-0.40, 2.79	0.75, 4.87	-4.24, 1.01
	Nominal p-value	-	-	0.2199
Change in 5-domain NPCCSS at 6 months	Mean change	0.48	1.60	-
	Mean difference	-	-	-1.11
	95% CI	-0.05, 1.02	0.86, 2.34	-2.03, -0.19
	Nominal p-value	-	-	0.0188

Changes in each individual domain of the NPCCSS (excluding hearing domain)	Mean change:			
	Ambulation	0.3	0.3	-
	Speech	-0.2	0.3	-
	Swallow	0.1	0.6	-
	Fine motor skills	0.2	0.6	-
	Cognition	0.3	0.1	-
	Eye movement	0.2	-0.1	-
	Memory	0.1	0.3	-
	Seizures	0.3	-0.1	-
Change in the NPC Clinical Database (NPC-CDB) score	Mean difference	-	-	-3.03
	95% CI	-	-	-9.90; 3.85
	Nominal p-value	-	-	0.3785
Change in Quality of Life (EQ 5D Y)	Better	-	-	0.4880
	Worse	-	-	0.1804
Change in the Scale for Assessment and Rating of Ataxia (SARA) score	Mean difference	-	-	0.74
	95% CI	-	-	-0.92; 2.40
	Nominal p-value	-	-	0.3710
Change in the Nine-Hole Peg Test (9HPT)	Mean difference	-	-	3.2
	95% CI	-	-	-15.71; 22.12
	Nominal p-value	-	-	0.7283
Clinical Global Impression Scale of Severity (CGI-S)	markedly or severely ill	51.8 %	33.4 %	-

Clinical Global Impression Scale - Improvement (CGI-I)	no change or minimally improved	70.4 %	53.3 %	-
	minimally worse	14.8 %	13.3 %	-
	much worse or very much worse	11.1 %	26.7 %	-
Oxysterol (cholestane-3β,5α,6β-triol)	Mean change	-7.450	-0.894	-
Un-esterified cholesterol	Mean change	29854.9	71725.6	-
HSP70	Mean change	1778.984	1022.393	-

Analysis description	**Primary Analysis: Open-label extension phase, data from the first 12 months**		
Analysis population and time point description	NPC patients from the double-blind study phase continued in the open-label phase; all patients were treated with arimoclomol together with standard of care treatment comparing baseline data (time point 0 = baseline 1) to 24 months (= 12 months open label phase).		
Descriptive statistics and estimate variability	Treatment group	Arimoclomol /Arimoclomol	Placebo/Arimoclomol
	Number of subject	26	15
	5 domain NPCCSS (change from baseline)	2.4	2.2
	standard deviation (SD)	4.3	3.6

Analysis description	**Secondary analysis: Open-label extension phase, data from the first 12 months**			
Analysis population and time point description	NPC patients from the double-blind study phase continued in the open-label phase; all patients were treated with arimoclomol together with standard of care treatment comparing baseline data (time point 0 = baseline 1) to 24 months (= 12 months open label phase).			
Effect estimate per comparison		Arimoclomol	Placebo	Arimoclomol vs Placebo
CGI-I	responder - yes:	59.1 %	61.2 %	-
Responder analysis if Patient's 5-domain NPCCSS	responder - yes	45.5%	46.2%	-
Time to worsening	median	17.8 months	17.7 months	-
	Nominal p-value			0.6029
Proportion of patients worsening	Worsening at 12 months - yes	50 %	46.2 %	-

	Nominal p-value			0.7184
Change in full scale NPCCSS apart from hearing domains	Mean change	3.7	3.2	-
Changes in each individual domain of the NPCCSS (excluding hearing domain)	Mean change:			
	Ambulation	0.4	0.5	-
	Speech	0.2	0.3	-
	Swallow	0.6	0.5	-
	Fine motor skills	0.6	0.8	-
	Cognition	0.6	0.2	-
	Eye movement	0.2	-0.1	-
	Memory	0.6	0.4	-
	Seizures	0.6	0.0	-
Change in the NPC Clinical Database (NPC-CDB) score	mean change	5.1	4.8	-
	SD	15.1	17.2	-
Clinical Global Impression Scale of Severity (CGI-S)	markedly or severely ill	40.9 %	30.8 %	-
Clinical Global Impression Scale - Improvement (CGI-I)	no change	27.2 %	42.6 %	-
	improved	31.8 %	23.1 %	-
	worse	40.9 %	30.8 %	-
Change in Quality of Life (EQ 5D Y)	mean	-6.0	0.8	-
	SD	20.2	16.2	-
Change in the Scale for Assessment and	mean	1.9	1.4	-

Rating of Ataxia (SARA) score	SD	4.7	5.5	-
Change in the Nine-Hole Peg Test (9HPT)	mean	-5.5	5.1	-
	SD	26.2	32.2	
Oxysterol (cholestane-3β,5α,6β-triol)	Mean change	-6.41	-4.75	-
Un-esterified cholesterol	Mean change	-43323	-24965	-
HSP70	Mean change	1040.0	903.24	-

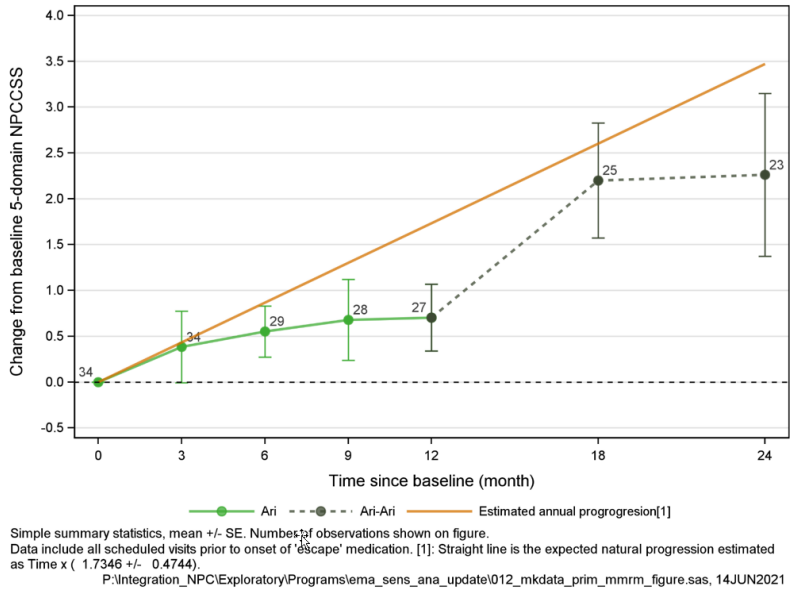
Analysis performed across trials (pooled analyses and meta-analysis)

In order to provide estimates for disease progression (as assessed by the 5-domain NPCCSS) under conditions without administration of arimoclomol (referred to as natural history progression), all 5-domain NPCCSS data from the observational trial CT-ORZY-NPC-001 and from the placebo patients of trial CT-ORZY-NPC-NPC-002 were combined and analysed using a random intercept- and slope- model.

A separate SAP was prepared for such Integrated Summary of Efficacy. Since CT-ORZY-NPC-001 was performed before CT-ORZY-NPC-002 and some of the patients were included in both trials, relevant output was to be generated showing data from both trials including the whole time-span. This was supposed to allow to assess potential compare in progression rate on randomised treatment in CT-ORZY-NPC-002 with no intervention in CT-ORZY-NPC-001 for those patients who participated in both trials. In total, 36 patients were enrolled in the observational trial (no treatment administered) CT-ORZY-NPC-001 of which 27 patients continued into the double-blind treatment phase of trial CT-ORZY-NPC-002. 23 newly accrued patients had been enrolled and randomised in CT.ORZY-NPC-002, where 7 of them where assigned to the placebo group (see Figure 3.2., Section Results – Participant Flow).

In order to evaluate persistence of the treatment benefit during 12 months of open-label extension, the expected placebo/natural progression rate in NPC as measured by the 5-domain NPCCSS was estimated. All available natural history data of disease progression as measured by 5-domain NPCCSS were combined, i.e. data from the observational trial CT-ORZY-NPC-001 were combined with the placebo data from trial CT-ORZY-NPC-002 in a post hoc analysis. Based on this combined data set, the estimated overall annual progression rate was 1.73 (± 0.47) (see linear model function in Figure below). When comparing the 24-months progression in the arimoclomol-arimoclomol group to the estimated placebo/natural progression of 3.46 points over 24 months, a treatment benefit of 1.06 was maintained.

Figure 5-1r **Change from Baseline in 5-domain NPCCSS for the Double-blind and Open-label Phases Combined (FAS, Patients Randomised to Arimoclomol)**



Source: [M5.3.5.3 Figure Hr]

Clinical studies in special populations

Controlled Trial NPC – 002	*Age at onset of disease*			Age above or below 4 years		Age above or below 12 years	
	Early infantile onset (3 months to <2 years)	***Late infantile onset (2 to < 6 years)***	***Juvenile onset (6 to < 15 years)***	**< 4 years**	**≥ 4 years**	**< 12 years**	**≥ 12 years**
Arimoclomol (n=34)	*6 (17.6%)*	*17 (50.0%)*	*11 (32.4%)*	*4 (11.8%)*	*30 (88.2%)*	*16 (47.1%)*	*18 (52.9%)*
Placebo (n=16)	*3 (18.8%)*	*7 (43.8%)*	*6 (37.5%)*	*2 (12.5%)*	*14 (87.5%)*	*11 (68.8%)*	*5 (31.3%)*

Supportive study(ies)

CT-ORZY-NPC-001

- Title of Study: A prospective non-therapeutic study in patients diagnosed with Niemann-Pick disease type C in order to characterise the individual patient disease profile and historic signo-symptomatology progression pattern
- Study Period:

- First patient screened: 09 October 2015
- First patient enrolled: 09 October 2015
- Last patient completed: 10 May 2017

- Primary objective:

  To characterise the individual patient disease progression profile (disease burden and progression) through the clinical, imaging, biological status, and Quality of Life prospectively recorded, together with the historic disease information collected from patient medical records.

- Number of patients:
  - Enrolled: 36
  - Completed: 31

Patients remained on their routine clinical care therapy, which for most patients included miglustat and did not receive any investigational drug product. Results from this observational trial confirmed the appropriateness of the population targeted for the trial CT-ORZY-NPC-002. The study was conducted at 12 sites in 7 countries: 1 in Denmark, 2 in Germany, 4 in Italy, 1 in Poland, 1 in Spain, 1 in Switzerland and 2 in the United Kingdom.

The patients had to participate in the study for 12-40 weeks and attend 2 study visits:

• Visit 1: Screening and Enrolment: Duration of 1-2 days;

• Visit 2: End of Study (EoS) visit: Performed 26 weeks (±14 weeks) after Visit 1 and had a duration of 1-2 days.

Overall, the patient populations included in the CT-ORZY-NPC-002 and CT-ORZY-NPC-001 trials were similar. Patients who had completed the observational trial, CT-ORZY-NPC-001, were eligible for the CT-ORZY-NPC-002 trial and could continue into the double-blind phase of this trial, and subsequently into the open-label extension phase.

Primary Objective

- To characterise the individual patient disease progression profile (disease burden and progression) through the clinical, imaging, biological status, and Quality of Life prospectively recorded, together with the historic disease information collected from patient medical records.

Secondary Objective

- To evaluate the safety data of the disease-related therapy and to record every adverse event (AE) linked to the disease.

The study endpoints relevant for efficacy were as follows:

• Clinical Status Endpoints:

- NPC clinical status scores (NPC Clinical Severity Scale [NPCCSS] and NPC "Stampfer" Score) to document the clinical progression of NPC;
- Quality of Life questionnaire applied to the patients (and/or the patients' parent[s]/legal guardian[s]).

• Biomarker Endpoints:

- As there are no validated biomarkers in NPC to evaluate disease progression burden and potential therapeutic response, the biomarkers were explorative to confirm clinical

observations and characterise the individual patient clinical status at both assessment time points. Absolute values in the listed biomarkers were recorded and analysed.

Overall, the mean age at baseline was 9.86 years, 15 (41.7%) of the patients were male, and the majority of the patients were White. The demographic characteristics are summarised in Table 2-2.

Table 2-2 Demographics – CT-ORZY-NPC-001 (All Enrolled Patients)

	Total (N=36)
Age; mean (SD)	9.86 (4.61)
Gender	
Male; n (%)	15 (41.7%)
Female; n (%)	21 (58.3%)
Race;	
White; n (%)	33 (91.7%)
Other; n (%)	3 (8.33%)
BMI; mean (SD)	18.06 (2.56)

Source: [CT-ORZY-NPC-001, Table 11-1]
BMI=Body mass index; SD=Standard deviation

All 36 enrolled patients had an NPC diagnosis with mutations in NPC1 and all patients had a history of neurological symptoms. The majority of the patients (30/36;83.3%) were treated with miglustat as part of their routine clinical care. The baseline disease characteristics are summarised in Table 2-3.

Table 2-3 Baseline Disease Characteristics – CT-ORZY-NPC-001 (All Enrolled Patients)

	Total (N=36)
NPC1 diagnosis; n (%)	36 (100%)
Time since first NPC symptom (years); mean (SD)	6.70 (3.70)
Currently treated with miglustat	
Yes	30 (83.3%)
No	6 (16.7%)
NPCCSS total score; mean (SD)	16.7 (9.6)
5-domain NPCCSS total score; mean (SD)	9.6 (6.0)
5-domain NPCCSS; individual domain scores	
Ambulation score; mean (SD)	2.0 (1.5)
Speech score; mean (SD)	1.6 (1.2)
Swallow score; mean (SD)	1.2 (1.7)
Cognition score; mean (SD)	2.7 (1.3)
Fine motor skills score; mean (SD)	2.0 (1.6)

Source: [CT-ORZY-NPC-001, Table 11-4, Table 11-7 to Table 11-13]
NPCCSS=NPC Clinical Severity Scale; SD=standard deviation

Clinical Status Endpoint

The results of the clinical status endpoints are summarised in Table 2-6.

Table 2-6 Change from Baseline in Clinical Status Assessments – CT-ORZY-NPC-001 (All Enrolled Patients)

	Visit 1 (Baseline)		Visit 2		Change from V1 to V2	
	N	Mean (SD)	N	Mean (SD)	N*	Mean (SD)
NPCCSS total score	36	16.7 (9.6)	32	18.6 (10.7)	32	2.7 (4.0)
5-domain NPCCSS total score	36	9.6 (6.0)	32	10.7 (6.6)	32	1.4 (2.9)
5-domain NPCCSS; individual domains						
Ambulation score	36	2.0 (1.5)	32	2.2 (1.7)	32	0.3 (0.7)
Speech score	36	1.6 (1.2)	32	2.0 (1.4)	32	0.3 (0.9)
Swallow score	36	1.2 (1.7)	32	1.4 (1.8)	32	0.4 (0.9)
Cognition score	36	2.7 (1.3)	32	2.7 (1.4)	32	0.0 (0.6)
Fine motor skills score	36	2.0 (1.6)	32	2.5 (1.8)	32	0.4 (1.1)
NPC-cdb	36	39.4 (20.0)	32	42.8 (21.8)	32	5.0 (7.9)

Source: [CT-ORZY-NPC-001, Table 11-7 to Table 11-13, and Table 11-15]
NPC-cdb=NPC-clinical database; NPCCSS=NPC Clinical Severity Scale; SD=standard deviation
* The number of patients contributing with Visit 2 data (N=32) differs from the number of completers (N=31), as one of the withdrawn patients had End of Trial/Visit 2 assessments performed at the day of withdrawal.

Quality of Life

In the assessment of the patients Quality of Life as captured by the EQ-5D-Y VAS score, there was a slight deterioration during the trial with a mean change of -4.0 (SD=18.6) from Visit 1 (68.8 [SD=19.9]) to Visit 2 (64.4 [SD=21.2]).

For the individual domains of the EQ-5D, the proportion of patients experiencing "some problems" or "a lot of problems" declined slightly from Visit 1 to Visit 2 in the domains selfcare and usual activities. The proportion of patients experiencing problems from Visit 1 to Visit 2 with regards to pain increased from 22.9 to 41.9%, and anxiety/depression increased from 30.6% to 41.9%. For the mobility domain, the proportion of patients experiencing problems were unchanged at the two visits.

Biomarkers

The key biomarkers measured are summarised in Table 2-7.

Table 2-7 **Summary of Biomarkers – CT-ORZY-NPC-001 (All Enrolled Patients)**

		Total (N=36)
Hsp70 in PBMC (pg/mL)		
Screening (Visit 1)	N	28
	Mean (SD)	1804.09 (713.67)
End of Trial (Visit 2)	N	24
	Mean	1469.94 (581.21)
Change from Visit 1 to Visit 2	N	20
	Mean	-448.29 (682.58)
Rate of Change per 6 months	Mean (SD)	-225.36 (411.76)
Healthy individuals*	Mean (SD)	12310.21 (4247.23)
Un-esterified Cholesterol in PBMC (ng/mg protein)		
Screening (Visit 1)	N	30
	Mean	77556.7 (21528.3)
End of Trial (Visit 2)	N	28
	Mean	98453.6 (99561.3)
Change from Visit 1 to Visit 2	N	23
	Mean	28056.5 (108522.2)
Rate of Change per 6 months	Mean (SD)	25943.72 (97557.45)
Healthy individuals*	Mean (SD)	76388.90 (33820.07)
Cholestane-triol (Oxysterols) in serum (ng/mL)		
Screening (Visit 1)	N	28
	Mean (SD)	88.31 (28.66)
End of Trial (Visit 2)	N	32
	Mean	88.52 (31.56)
Change from Visit 1 to Visit 2	N	26
	Mean	3.52 (14.92)
Rate of Change per 6 months	Mean (SD)	2.64 (10.69)
Healthy individuals*	Mean (SD)	5.97 (1.13)

Full analysis set

Source: [CT-ORZY-NPC-001, Table 11-23]; [Addendum to CT-ORZY-NPC-001, Table 4-1 and Table 4-2]

*Healthy individuals: >25 years, no known hepatic, renal, cardiac or metabolic disorders. No hepatitis or HIV (HSP70: n=19; Unesterified cholesterol: n=6; Cholestane-triol: n=3). Source: [8292274], [8327375], [8314550]

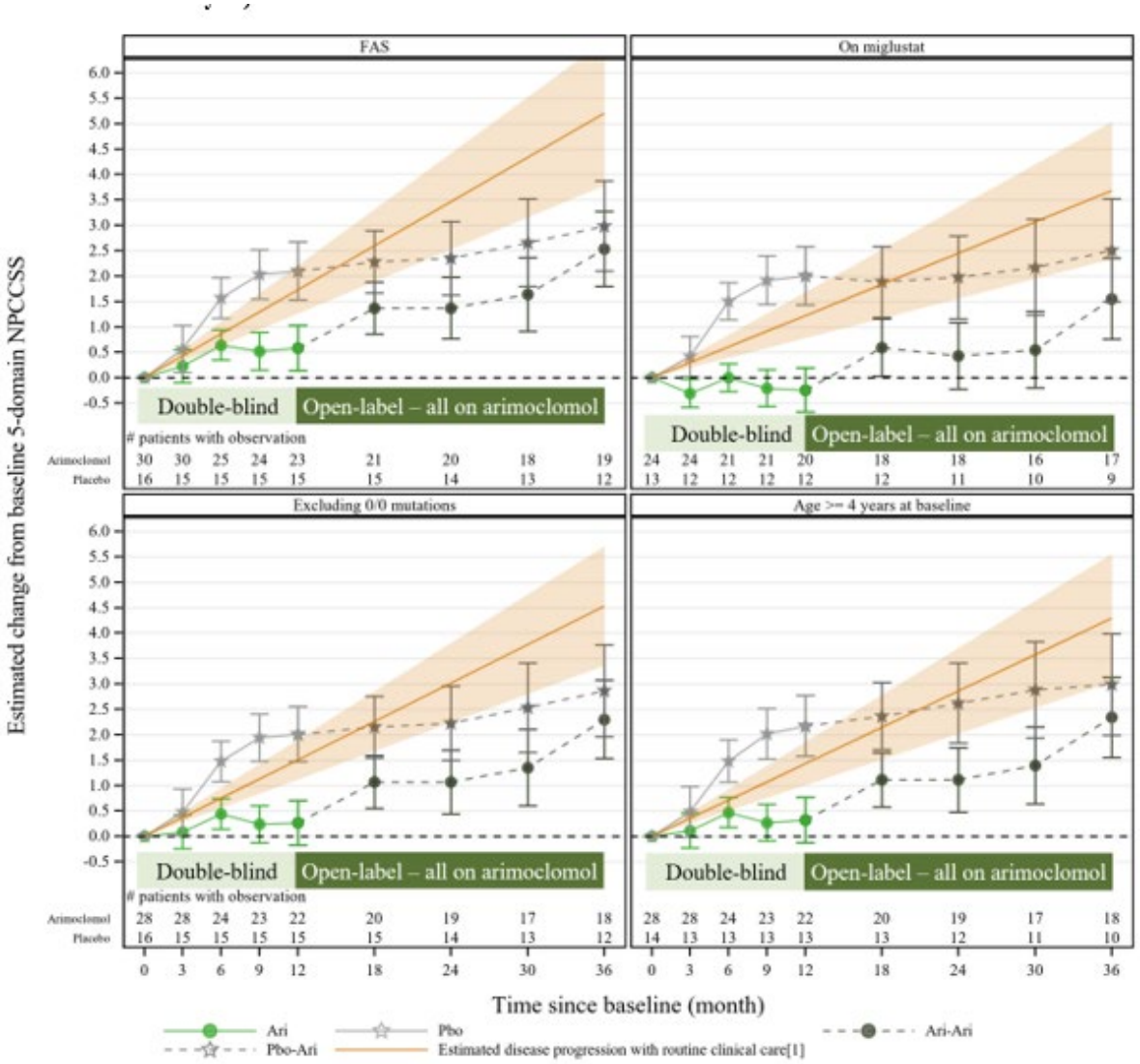
3.3.5. Additional data provided in D120 responses

The following new figures/tables were provided by the applicant in the scope of d120 responses

1. Post-hoc analysis excluding patients with aggressive disease progression:

As requested by the Rapporteur during the clarification meeting, a post-hoc analysis was performed excluding the 4 patients with a more aggressive progression pattern (Figure 2 13).

Figure 2-13 **Estimated change from baseline to Month 36 in 5-domain NPCCSS for full population, subgroup with miglustat use at baseline, subgroup ≥4 years at baseline, and subgroup excluding patients with double null mutations (FAS excluding 4 patients with aggressive progression, post-hoc analysis)**



LSMs of an 'adapted' MMRM model including open label data at 18 and 36 months, respectively. The adaptation is to include a two-level factor signifying 'blinded' and 'open label' periods, respectively. This factor is then interacting with all effects in the model's mean structure to achieve 'period specific' LSMs. The covariance matrices are unstructured and independently specified for the two periods. Data include all scheduled visits prior to onset of 'escape' medication. Number of observations shown on figure. [1]: Straight line is the expected disease progression with routine clinical care estimated as Time x (rate pr year +/- SE).

2. Enhanced benefit in the subgroup with miglustat use at baseline:

In contrast to the small subgroup of 11 patients without miglustat treatment at baseline, the baseline demographics and disease severity were more balanced between the arimoclomol and placebo groups for the larger subgroup of 39 patients with use of miglustat at baseline (Table 2 4).

Table 2-5 **Analysis of change from baseline to Month 12 in 5-domain NPCCSS in full population and subgroup with use of miglustat at baseline (FAS)**

	Arimoclomol	Placebo	Arimoclomol versus placebo LS means difference (95% CI)	p-value
Full population	27	15	-1.40 (–2.76; -0.03)	0.0456
Subgroup with use of miglustat at baseline	22	12	-2.06 (-3.49; -0.63)	0.0060

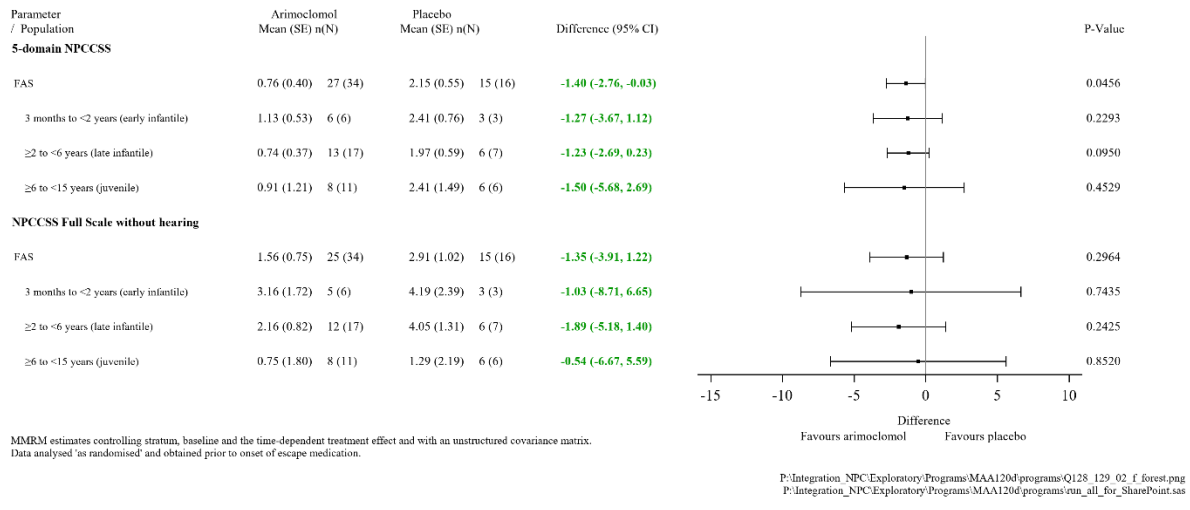
CI = confidence interval; FAS = full analysis set; N = number of patients in FAS; n = number of patients included in the analysis; NPCCSS = NPC Clinical Severity Scale

Source: Figure 2-6 and Figure 2-7.

3. Onset of neurological symptoms:

Figure 2 17 shows the analysis of change from baseline to Month 12 in the 5-domain and full-scale NPCCSS in subgroups based on age at first neurological symptom.

Figure 2-17 **Analysis of change from baseline to Month 12 in 5-domain and full-scale NPCCSS in subgroups based on age at first neurological symptom (FAS)**



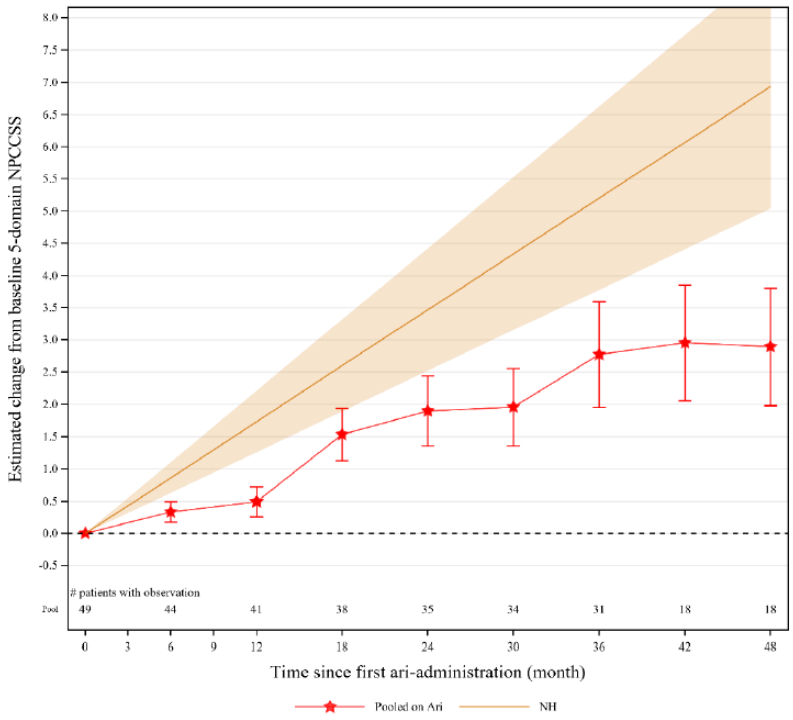
FAS = full analysis set; N = number of patients in full population/subgroup; n=number of patients with data; NPCCSS = NPC Clinical Severity Scale; SE = standard error.

The 2 protocol-specified groups <3 months and 3 months to <2 years were collapsed into one group due to the low number of patients in this age span.

3.3.6. Additional data provided in D180 responses

Interim CTR of the 36-months data (12 months double-blind and 24 months open-label treatment) and preliminary 48-months data (12 months double-blind and 36 months open-label treatment) were provided by the applicant.

Figure 3-3 **MMRM estimated change in 5-domain NPCCSS from initiation of arimoclomol treatment to Month 48 in all patients receiving arimoclomol during NPC-002 – full population**



3.3.7. Discussion on clinical efficacy

For efficacy evaluation, trial CT-ORZY-NPC-002 was considered the main source of evidence. This trial consisted of two parts, a randomised, double-blind placebo-controlled 1-year treatment (DB) phase and an open-label extension (OLE) phase in which all patients received arimoclomol and for which initially 12 months data have been provided by the applicant. Interim CTR of the 36-months data (12 months double-blind and 24 months open-label treatment) and preliminary 48-months data (12 months double-blind and 36 months open-label treatment) were provided by the applicant in the D180 responses. The applicant stated that it might be shortened in case of "earlier US/EU marketing authorisation of arimoclomol". This was of concern because of (1) the importance of the data from this phase of the trial and (2) the limited number of participants in the trial in general. The applicant explained that currently all patients included in the OLE (n=32) have already completed 24 month of the OLE phase, and OLE phase is considered finalised in Q2 2022 (last patient last visit, day 60). A recent examination has shown that only 5/32 participants would profit from commercially available arimoclomol and are therefore at risk to leave the trial prematurely as soon as arimoclomol gets marketing authorisation. Furthermore, there is no information indicating that these 5 patients will not remain in the trial until completing day 60 of the OLE. Hence, data from the majority of all patients included in the OLE phase will be available, which is endorsed. The primary objective of the study was to evaluate therapeutic response to arimoclomol versus placebo, both in addition to best available standard of care, at 12 months for the DB phase and long-term therapeutic response of arimoclomol in

patients with NPC at 18, 24, 30, and 36 months in the OL extension phase. In summary, the trial objectives and endpoint are acceptable and meaningful and were also agreed in previous scientific advice procedures. The same is true with respect to the characterisation of the target population by the inclusion and exclusion criteria, randomisation and blinding procedures used.

The primary efficacy endpoint was changed during trial conduct from the overall NPCCSS score to a reduced 5-domain NPCCSS score (change to baseline after one year). The decision for the endpoint change was primarily driven by authorities' requests for simplification of outcome evaluation. Validation of the 5-domain NPCCSS score contained also independent work packages, primarily in the qualitative part where the five domains of primary relevance were identified together with patients and caregivers. According to this part of the validation work, the top 3 symptoms that would matter most in an NPC patient population (similar to that enrolled in trial CT-ORZY-NPC-002) were claimed to be ambulation, cognitive impairment, and swallowing difficulties. In context of the interpretation of the actual trial outcome, it is important to note that in two of these top 3 symptom domains (i.e. cognition and ambulation) no relevant change to baseline after one year of arimoclomol treatment could be seen based on the placebo comparison. The overall effect seen at 12 months supporting a trend in favour of arimoclomol treatment on the 5-domain scale was primarily driven by signals of slowed disease state progression in the domains of 'swallowing' and 'speech'. It is hence important to note that the small benefit seen in the FAS at 12 months with borderline clinical relevance/statistical significance is not equally attributable to the 5 domains covered in the primary endpoint, but basically down to 2/5 domains. It is also to note, that for all 5 domains, a high proportion of patients remained stable in both treatment groups and there were changes in severity seen in both directions, predominantly in terms of worsening. However, due to the heterogeneity of the disease as well as the variability in the progression of individual domains, an assessment of treatment effects based on single symptom domains fails to capture the course of the disease, and treatment effect is unlikely to be demonstrated at the level of single domains. Therefore, the use of a composite score is considered justified. Although the primary efficacy endpoint is statistically significant after corrections of baseline data of one patient, the effect observed in the full analysis set is still borderline, and robustness of the effect estimates for the primary endpoint is questioned. Nevertheless, the fact that this is a rare disease and only limited sample size could be included in the study as well as the fact that miplyffa is not a cure but rather slowing disease progression are extremely limiting factors and are acknowledged. Independent studies/surveys as well as NPC experts and key opinion leaders concluded that a 1 point change as well as slowing of disease by 30-50% reduction in rate of progression is considered meaningful and clinically relevant. The effect seen is enhanced and statistically significant (p=0.0060) in the subgroup including the majority of study participants, the group co-treated with miglustat. This is also the group in which baseline 5-domain NPCCSS values are similar and comparable in placebo and arimoclomol-treated group, hence the result of this analysis, even though it was an exploratory subgroup analysis, should not be ignored. However, as discussed below, additive effect of arimoclomol could not convincingly be shown, and registration of arimoclomol cannot be based solely on efficacy in miglustat subgroup. **(MO)**

Overall, the patient population was quite heterogeneous regarding the 5-domain NPCCSS score in both groups; mean baseline scores were, however, higher in the arimoclomol group compared to placebo for all 5 domains, and higher frequency of protein mutations, particularly patients with double functional null, were seen in arimoclomol group, meaning that patients randomised to arimoclomol group performed worse and had worse disease prognosis compared to patients included in the placebo group, which might also impact on the interpretability of the results. Using change from baseline to 12 months in 5-domain NPCCSS and also full scale NPCCSS rather than raw data accounted already for the imbalances in disease severity, when defining the estimands for the analyses of the double-blind phase of the trial. However, other (unknown) factors such as double functional null mutations indicative of a more aggressive disease course were not considered. Since 3 patients harbouring

double functional null mutations were randomised only into the arimoclomol group, a post-hoc subgroup analysis excluding these patients was provided and revealed a larger effect size (arimoclomol vs placebo LS means difference: FAS = -1.40, p = 0.0456; posthoc analysis excluding double functional null mutations = -1.61, p = 0.0201). However, this is based on post-hoc analysis, and excluding patients from the small patient cohort included in the study is seen very sceptical.

With regard to judgement of clinical relevance of the effect seen on the 5-domain scale in comparison to placebo (point estimate of change to baseline difference to placebo: -1.40 points on the scale), the context of the validation information provided concerning anchoring with CGI-I seems relevant. Whilst validation work revealed noteworthy correlation between the 5-domain score and CGI-I, it was reported that disease state worsening identified by CGI-I corresponded to a mean change of ~ 2.6 points on the 5-domain scale (median 2.0). In light of this association, the fact that the observed small treatment effect in trial CT-ORZY-NPC-NPC-002 could not be seen in the key secondary endpoint CGI-I does not come unexpected. It seems that the 5-domain NPCCSS score is more sensitive to changes as compared to most (key) secondary endpoints, from which none could eventually reflect the effect seen in the primary endpoint using the FAS. However, it has to be noted that CGI score was originally designed to capture disease severity in psychiatric patients and that the use of this score is questionable due to the following reasons: 1) CGI is not validated for slowly progressing disorder such as NPC, 2) CGI has a lower sensitivity to change, 3) CGI was introduced late in the clinical trial resulting in an incomplete CGI dataset. Although, a correlation between CGI and 5-domain NPCCSS could be shown in the responder analysis at the beginning of the trial, the CGI scale failed at later stages. The design of the score together with the data derived from the clinical trial indicate that the selection of CGI as a key secondary endpoint in an NPC trial remains questionable. Regarding effect seen in other secondary endpoints, the applicant provided data on outcomes developed for use in NPC patients ('NPC-specific endpoints') and those developed for use in other indications ('non-NPC-specific endpoints'). The first category included the full-scale NPCCSS (excluding hearing domains) and the NPC clinical database (NPC-cdb). Even though both NPC-specific endpoints were in favour of arimoclomol, they do not show statistical significance. Overall support from secondary endpoints is rather weak in the full population, a clear trend can be observed in miglustat co-treated patient cohort.

Evidence of persistence of efficacy in the OLE phase is currently still of major concern. It remains difficult to differentiate whether the stabilisation of the score values was due to an arimoclomol effect or due to the natural disease course, and the extent of bias in the comparison with external controls is unclear. The persistence of the treatment benefit beyond 12 months should leverage the randomisation in study 002 and allow considering the RCT part of study 002 together with its open-label extension part as a "randomised start design". In order to demonstrate maintenance of effect after 1 year treatment, the applicant should compare the treatment difference at the 1-year time point (end of placebo-controlled phase) to the treatment difference at the 2-year time point (or likewise the changes in the second year between the Miplyffa-Miplyffa vs Placebo-Miplyffa arms). Differences in these effect estimates should be discussed, and graphical presentation should be used to facilitate the interpretation. The potential selection bias (due to patients not rolling over to the OLE, or generally withdrawing from the study) should be addressed, e.g. by making reasonable assumptions for those who are not followed up. The assumptions should be justified and the robustness of the estimates with respect to deviation from those assumptions should be evaluated by sensitivity analysis. This analysis investigating the maintenance of the effect should not rely on an assumption of linearity over time but use the mixed model in analogy to the pre-specified primary analysis, i.e. include visit as fixed effects along with a treatment-by-visit interaction term.**(MO)**

Another major concern was extrapolation of study results to the broad population as expressed in the proposed indication. Patients aged from 2-18 years and 11 months have been included in this study. According to the applicant this age range was chosen for 2 reasons: (1) to reduce further

heterogeneity in the study population with regard to the expectably small sample size (see also a previous discussion in EMA scientific advice EMEA/H/SA/3709/1/2017/PA/SME/III) and (2) to enrich for patients who are likely to progress measurably over an observation period of 12 months and hence allow for reliable assessment of a potential treatment benefit. In general, it can be concluded from published literature that the same pool of symptoms, which can be mapped to the 5 individual symptom domains of the 5-domain NPCCSS, is relevant across patients independent of age. However, concerning the interpretation of efficacy results of arimoclomol, the age of onset is a much more relevant factor than patient's actual age, because early onset of the disease implicates a higher risk for a more aggressive disease course. In subgroup analyses provided by the applicant, patients were pre-specified based on the age at first neurological symptoms. The applicant provided additional data showing change from baseline to month 12 in subgroups based on age at the first neurological symptom; no noticeable difference between the effect of arimoclomol in early infantile, late infantile, and juvenile types of NPC in both 5-domain and full-scale NPCCSS could be demonstrated. However, 3 out of 4 patients in the subgroup <4 years at baseline have an early aggressive disease course due to the double functional null mutations. These were all randomised to active treatment. From Figure 2-18 it seems that the two patients in this subgroup <4 years on placebo remain quite stable over time. Thus in essence the same arguments as discussed before are valid (i.e. differentiation between treatment vs natural disease progression) and the extrapolation is not considered justified. The general argument that treatment should start early in neurodegenerative diseases is acknowledged, given that a treatment is efficacious. As efficacy is not considered established in the ITT (see above), the extrapolation to adults is currently not considered justified.

Of note, all patients had mutations in NPC1 gene, which represents 95% of all cases, whereas NPC2 mutations are extremely rare (5% of all cases). However, in both cases (NPC1 and/or NPC2 mutation), NPC proteins are often misfolded and degraded prematurely, leading to impaired lysosomal function and accumulation of multiple lipid species. Even though patients with NPC2 mutated are not included in the current dataset, differences regarding the treatment effect of arimoclomol are not expected due to the mode of action of the drug and the similar pathophysiological mechanism.

In the clinical trials of the development programme, patients receiving arimoclomol were still on standard of care therapy; the majority of patients were treated with miglustat. It is noteworthy, that 11 patients did not receive miglustat as standard of care medication. In the EU, miglustat is approved for treatment of NPC patients, however, in the US, miglustat is currently not approved for this indication. In order to allow study protocol approval by FDA, it was decided to include patients not treated with miglustat. Thus, also European patients who were not candidates for miglustat treatment (age recommendation, EU countries in which miglustat is currently not offered as standard of care treatment) could be included in the study. However, in the majority of patients, arimoclomol was tested as add-on therapy rather than as an individual therapy.

On the one hand, treatment effect observed in patients using miglustat at baseline showed a mean difference in change from baseline to Month 12 in 5-domain NPCCSS of -2.06 (95% CI: -3.49; -0.63; p = 0.0060), which was more pronounced than effect observed in the FAS (-1.4). On the other hand, conclusions on the effect of arimoclomol used as monotherapy cannot be drawn based on the presented data provided from the DB phase. First of all, number of patients in the non-miglustat group is extremely limited (placebo: n=3, arimoclomol: n=8), and secondly, there were several imbalances in baseline data (baseline disease score as measured by 5-domain NPCCSS in placebo vs armicolcomol group: 8.7 vs 13.3; 3 patients with double functional null mutation indicating an aggressive disease course included in arimoclomol group only) making it difficult to compare non-miglustat placebo with non-miglustat arimoclomol cohort, and hence, a conclusion on effectiveness of arimoclomol in patients not treated with miglustat cannot be given. Overall, additive or synergistic effect of arimoclomol and miglustat could not be convincingly demonstrated. Whether or not the enhanced effect seen in the

primary and NPC specific secondary endpoints is due to additive/synergistic effect or down to the fact that baseline characteristics were better balanced leading to better comparison of placebo and arimoclomol treated group, is currently unknown. **(MO)**

These other concerns were especially noteworthy to be discussed here:

1) Formal dose-response studies were not performed by the applicant, neither investigation of optimal dose nor investigation of dose intervals. The dose used in study CT-ORZY-NPC-002 was solely selected based on nonclinical safety ratio assumptions. Within the scope of an EMA scientific advice, the applicant was already previously advised (EMEA/H/SA/3709/1/FU/1/2019/PA/SME/III) that the proposed dosing regimen, ranging from 150 mg to 600 mg/d depending on pre-defined body weight bands should be adequately justified. NPC represents a very rare disease, hence, formal dose finding studies could not be perfomed. Therefore, an allometric scaling method from Phase 1 PK data was used. The dosing regimen based on bodyweight and also the daily exposure limit are justified based on a safety factor of 2 compared to the No observed effect level in rats. The applicant justified selected dose used in clinical studies; arimoclomol in the given dose was well tolerated and an effect could be observed, especially in miglustat treated patients.

2) The applicant claims that biomarker evidence from baseline to 12 months supported the clinical results presented in this dossier. The changes in the key biomarkers are, however, considered borderline, and also the clinical impact remains inconclusive. Three key biomarkers were selected in the supportive study CT-ORZY-NPC-001: HSP70, un-esterified cholesterol, and cholestane-triol, however, it was also shown in the same study that 2/3 ((HSP70 and un-esterified cholesterol) do not correlate with the severity of the disease.

Additional information was provided specifying that all biomarkers used can be subdivided into two categories: 1) biomarkers related to disease pathology (e.g. unesterified cholesterol and cholestane-triol) and 2) biomarkers related to the mechanism of the drug (HSP70), whereas the biomarker Lyso-SM-509, which was added as an amendment to study protocol 7, is related to both. Pharmacodynamic markers such as HSP70 do not necessarily correlate with disease severity and hence, no correlation with changes in the 5-domain NPCCSS could be observed. However, even as a marker for arimoclomol activity, only borderline increase (except for 2 outliers) was shown for HSP70. On the other hand, disease pathology is highly correlated to lysosomal lipid accumulation and thus, NPC patients show elevated levels of cholestane-triols and unesterified cholesterol. There is a trend in reduction of both biomarkers upon arimoclomol treatment, however, it is lacking statistical significance. It is argued that this might be a result of short trial duration and biological variability within the analysed sample. The biomarker Lyso-SM-509, which relates to both drug mechanism and disease pathology, was introduced later in the study protocol and therefore, these data were not available at the time of submission of the MAA. According to literature, plasma Lyso-SM-509 levels correlate with NPCCSS and also other biomarkers specific for NPC. Arimoclomol treatment significantly reduced Lyso-SM-509 levels at 12 months compared to placebo, even though there is high interindividual variability. These results support the predicted mechanism of action and, thus, a potential for clinical effects could be expected. However, taken together, the pharmacological rationale and evidence on biological plausibility to support the efficacy in miglustat subgroup is weak, indicating lack of credibility of efficacy in miglustat subpopulation. As the application is based on a single RCT, and the replication of study results cannot be made, biological plausibility and data from subgroup should be exceptionally strong.

3.3.8. Conclusions on clinical efficacy

In conclusion, effect of arimoclomol is still not convinvingly demonstrated.

Currently, there are two major objections:

- Efficacy has not been sufficiently demonstrated
- Uncertainty of maintenance of effect of arimoclomol in the OLE study

3.3.9. Clinical safety

3.3.9.1. Patient exposure

CT-ORZY-NPC-002 Double-blind + Open label Phase (Pivotal Study in NPC Patients)

A total of 34 patients were randomised to arimoclomol treatment and 16 patients to placebo treatment. A total of 27 patients (79.4%) in the arimoclomol group and 15 patients (93.8%) in the placebo group completed the blinded phase of the trial (Table 5-1).

A total of 41 patients were exposed to arimoclomol treatment in the open-label extension phase; out of these, 26 patients were exposed to arimoclomol in the double-blind phase (arimoclomol-arimoclomol group) and 16 patients received placebo (placebo-arimoclomol group). A total of 22 patients in the arimoclomol-arimoclomol group and 12 patients in the placebo-arimoclomol group completed the 24 months trial visit (Table 5-1).

Table 5-1 Overview of Exposure in CT-ORZY-NPC-002 (DB and DB+OL)

	Arimoclomol 372 mg weight-adjusted	Placebo/ Arimoclomol 372 mg weight-adjusted	Placebo
DB Phase			
Exposure (days)			
N	34		16
Mean (SD)	306.9 (107.7)		332.6 (90.1)
Duration (N,%)			
Duration of Exposure < 4 Weeks			1 (6.3)
Duration of Exposure ≥ 4 Weeks	34 (100.0)		15 (93.8)
Duration of Exposure ≥ 12 Weeks	32 (94.1)		15 (93.8)
Duration of Exposure ≥ 26 Weeks	29 (85.3)		15 (93.8)
Duration of Exposure ≥ 52 Weeks	10 (29.4)		5 (31.3)
DB + OL			
Exposure (days)			
N	26	15	41
Mean (SD)	688.8 (68.1)	332.7 (72.4)	558.5 (186.8)
Duration (N,%)			
Duration of Exposure ≥ 4 Weeks	26 (100.0)	15 (100.0)	41 (100.0)
Duration of Exposure ≥ 12 Weeks	26 (100.0)	15 (100.0)	41 (100.0)
Duration of Exposure ≥ 26 Weeks	26 (100.0)	13 (86.7)	39 (95.1)
Duration of Exposure ≥ 52 Weeks	26 (100.0)	4 (26.7)	30 (73.2)
Duration of Exposure ≥ 78 Weeks	24 (92.3)		24 (58.5)
Duration of Exposure ≥ 104 Weeks	4 (15.4)		4 (9.8)

N: Number of patients, %: Percentage of patients, SD: Standard deviation. Single PK dose not included.
Source: [M5.3.5.3 Safety NPC002 Tables 1.1.1, 1.1.2 and NPC002 DBOL Tables 1.1.1 and 1.1.2]

Age group distribution:

Table 5-1 Baseline Age Group Distribution – CT-ORZY-NPC-002 (Double-blind Phase)

	Arimoclomol 372 mg weight-adjusted	Placebo
Age < 4 Years	4	2
4 Years ≤ Age < 12 Years	12	9
12 Years ≤ Age < 18 Years	13	5
18 Years ≤ Age < 19 Years	5	-

N: Number of patients.
Source: [M5.3.5.3 NPC002 Tables 1.17.1, 1.17.2, 1.17.3, 1.17.4]

Concomitant medications:

In the subgroup of patients using miglustat as concomitant therapy, the baseline demographics were more similar for the arimoclomol and placebo groups (Table 10-6).

Table 10-6 Baseline Demographics in the Subgroups of Patients on or Without Concomitant Miglustat Therapy

		Arimoclomol	Placebo	Arimoclomol	Placebo
Subgroups		Not on Miglustat (n=8)	Not on Miglustat (n=3)	On Miglustat (n=26)	On Miglustat (n=13)
Age (years)	Mean (SD)	7.0 (5.4)	15.0 (1.7)	12.8 (4.7)	9.1 (3.6)
Sex	Male	5 (62.5%)	2 (66.7%)	12 (46.2%)	5 (38.5%)
	Female	3 (37.5%)	1 (33.3%)	14 (53.8%)	8 (61.5%)
BMI (kg/m²)	Mean (SD)	17.19 (1.45)	22.03 (4.28)	19.23 (4.57)	18.78 (3.06)

Exposure in Other Indications

Table 5-2 Overview of Exposure in Completed Trials in Other Indications

	Arimoclomol 47-372 mg/day	Placebo
Safety set (N,%)	97 (100.0)	49 (100.0)
Exposure (days)		
Mean (SD)	110.9 (81.9)	161.5 (124.0)
Duration (N,%)		
Duration of Exposure < 4 Weeks	7 (7.2)	
Duration of Exposure ≥ 4 Weeks	90 (92.8)	49 (100.0)
Duration of Exposure ≥ 12 Weeks	78 (80.4)	42 (85.7)
Duration of Exposure ≥ 26 Weeks	9 (9.3)	13 (26.5)
Duration of Exposure ≥ 52 Weeks	4 (4.1)	8 (16.3)
Duration of Exposure ≥ 78 Weeks		1 (2.0)

N: Number of patients, %: Percentage of patients, SD: Standard deviation
Source: [M5.3.5.3 Safety Pooled Tables 1.50.3 and 1.50.4]

Overall Exposure in all completed trials

Table 1-3 Overview of Exposure – All completed trials

	Arimoclomol	Placebo
Safety set (N,%) [*]	280 (100.0)	94 (100.0)
Exposure (days)		
N	280	94
Total days	46553	13501
Mean (SD)	166.3 (205.0)	143.6 (145.7)
Min - Max	1 - 777	1 - 565
Duration		
Duration of Exposure < 4 Weeks	110 (39.3)	26 (27.7)
Duration of Exposure ≥ 4 Weeks	170 (60.7)	68 (72.3)
Duration of Exposure ≥ 12 Weeks	149 (53.2)	57 (60.6)
Duration of Exposure ≥ 26 Weeks	97 (34.6)	28 (29.8)
Duration of Exposure ≥ 52 Weeks	35 (12.5)	13 (13.8)
Duration of Exposure ≥ 78 Weeks	24 (8.6)	1 (1.1)
Duration of Exposure ≥ 104 Weeks	4 (1.4)	

N: Number of patients, %: Percentage of patients, SD: Standard deviation,
[*] A patient receiving different treatments during the trial counts as part of safety set for all relevant treatments.
Including trials: CT- ORZY-NPC-002 (DB+OL), AALS-001 (DB), AALS-001 (OL), ALS SOD1, IBM10656, Trial 40338, Trial 40343, AALS-002, AALS-004, AALS-011, AALS-005, AALS-010, OR-ARI-MET-01)
Source: [M5.3.5.3 Pooled Tables 1.50.1 and 1.50.2]

3.3.9.2. Adverse events

CT-ORZY-NPC-002 Double-blind Phase

The overall proportion of patients who had reported TEAEs was similar for the arimoclomol (88.2%) and placebo (81.3%) groups (Table 12-1).

A higher proportion of patients in the placebo group compared with the arimoclomol group reported severe TEAEs and SAEs. One fatal event was reported in the trial in a patient in the arimoclomol group.

A higher proportion of patients in the arimoclomol group than in the placebo group reported TEAEs assessed as IMP-related by the investigator, a higher proportion reported AEs of special interest (gastrointestinal events) and a higher proportion reported events leading to trial drug discontinuation.

Table 12-1 Summary of TEAEs: Continuous Dose Period (Safety Set)

	Arimoclomol (N=34)		Placebo (N=16)		Total (N=50)	
	E	n (%)	E	n (%)	E	n (%)
Any Treatment-Emergent Adverse Event	277	30 (88.2%)	92	13 (81.3%)	369	43 (86.0%)
Severe Treatment-Emergent Adverse Event	9	4 (11.8%)	8	4 (25.0%)	17	8 (16.0%)
Serious Treatment-Emergent Adverse Event	9	5 (14.7%)	10*	6 (37.5%)	21*	11 (22.0%)
Drug-Related Treatment-Emergent Adverse Events	38	12 (35.3%)	3	3 (18.8%)	41	15 (30.0%)
Serious Drug-Related Treatment-Emergent Adverse Events	3	2 (5.9%)	0	0	3	2 (4.0%)
Treatment-Emergent Adverse Events related to Trial Procedures	0	0	0	0	0	0
Treatment-Emergent Adverse Events related to Trial Disease	63	19 (55.9%)	19	6 (37.5%)	83	25 (50.0%)
Treatment-Emergent Adverse Events leading to Trial Drug Discontinuation	4	3 (8.8%)	0	0	4	3 (6.0%)
Treatment-Emergent Adverse Events leading to death	1	1 (2.9%)	0	0	1	1 (2.0%)
Treatment-Emergent Adverse Events of Special Interest	75	21 (61.8%)	15	6 (37.5%)	90	27 (54.0%)

*In error, Patient ID (placebo) was categorised in the statistical analyses as having 2 SAEs (*epilepsy* and *respiratory tract infection*) in the continuous dose period; however, the events actually occurred between the single dose period and the continuous dose period. Hence, the number of SAEs in the placebo group is 10 events and the total number of SAEs is 19 events in the continuous dose period.

The table presents number of events (E) and number and percentae of patients (n (%)).

The denominator for each percentage is the number of patients within the column.

CT-ORZY-NPC-002 Open label Phase

A total of 87.8% of the patients reported at least 1 TEAE; 26.8% reported at least 1 serious TEAE during the open-label extension period. TEAEs were reported in 92.3% of the patients in the arimoclomol-arimoclomol group and 80% of those in the placebo-arimoclomol group (Table 2-4).

Serious TEAEs were reported in 34.6% of patients in the arimoclomol-arimoclomol group and 13.3% of those in the placebo-arimoclomol group.

Table 2-4 Summary of Adverse Events - CT-ORZY-NPC-002 (Open-Label Phase)

	Arimoclomol 372 mg weight-adjusted/ Arimoclomol 372 mg weight-adjusted N (%) E	Placebo/ Arimoclomol 372 mg weight-adjusted N (%) E	Arimoclomol Total N (%) E
Safety set (N,%)	26 (100.0)	15 (100.0)	41 (100.0)
TEAEs	24 (92.3) 114	12 (80.0) 48	36 (87.8) 162
Serious TEAEs	8 (30.8) 17	2 (13.3) 2	10 (24.4) 19
Non-serious TEAEs	24 (92.3) 97	12 (80.0) 46	36 (87.8) 143
TEAEs leading to withdrawal from IMP	2 (7.7) 3	1 (6.7) 2	3 (7.3) 5
AEs with fatal outcome	1 (3.8) 1		1 (2.4) 1
Severity of TEAEs			
Mild	20 (76.9) 54	9 (60.0) 27	29 (70.7) 81
Moderate	17 (65.4) 44	5 (33.3) 21	22 (53.7) 65
Severe	9 (34.6) 16		9 (22.0) 16
Relationship of TEAEs			
Probably related	1 (3.8) 1	1 (6.7) 1	2 (4.9) 2
Possibly related	2 (7.7) 2	3 (20.0) 4	5 (12.2) 6
Not related	24 (92.3) 111	11 (73.3) 43	35 (85.4) 154
Relationship of serious TEAEs			
Probably related	1 (3.8) 1		1 (2.4) 1
Not related	8 (30.8) 16	2 (13.3) 2	10 (24.4) 18

To further support the safety evaluation of arimoclomol and enhance signal detection, TEAEs reported in the CT-ORZY-NPC-002 DB phase was compared with those reported in the DB completed clinical trials in Other Indications.

Since all DB trials with arimoclomol were different in duration (12 months vs 3-12 months), the comparison is performed using 2 different data presentations, exposure-adjusted incidence rate and unadjusted incidence by SOC and PT.

The exposure-adjusted incidence rate is influenced by the timing of the first event for an individual whereas the unadjusted incidence is influenced by the duration of the trial while.

The comparison between the TEAE profiles reported in NPC and Other Indications is further complicated by the difference age (children vs adults), disease characteristics, and the difference in dose (arimoclomol 372 mg weight-adjusted vs arimoclomol 47-372 mg; fixed doses).

Comparing the TEAEs from the CT-ORZY-NPC-002 trial with those reported in other indications did not enhance the signal detection, as the results in the two groups were quite different:

Based on the exposure adjusted incidence rate comparison the following PTs were slightly more frequently reported in the arimoclomol group the placebo group (Table Incidence rates, below):

Incidence Rates - CT-ORZY-NPC-002 (Double-Blind Phase) and Other Indications

	CT-ORZY-NPC-002 (DB)		Other Indications	
	Arimoclomol 372 mg weight-adjusted	Placebo	Arimoclomol 47-372 mg	Placebo
	N IR	N IR	N IR	N IR
Safety set (N,%)	34 (100.0)	16 (100.0)	97 (100.0)	49 (100.0)
Any treatment emergent adverse event	30 609.1	12 224.9	85 905.7	41 1072.7
Dry mouth			9 29.8	2 8.8
Dizziness			5 15.9	
Tremor	3 10.9			
Creatinine renal clearance decreased			8 25.0	1 4.3
Weight decreased	5 19.0			2 9.0
Insomnia			8 25.4	2 9.2
Urticaria	3 10.4			
Decreased appetite	3 11.1		3 9.4	4 18.2

DB: Double-blind,
N: Number of patients, IR: Exposure adjusted incidence rate, SOC: System organ class, PT: Preferred term
Exposure adjusted event rate is defined as the total number of events divided by the sum of exposure (years)
Coding Dictionary: MedDRA 19.0
Source: [M5.3.5.3 Pooled Table 1.51.1]

Adverse events by system organ class

CT-ORZY-NPC-002 Double-blind Phase

The SOCs with an overall incidence of TEAEs>40% in either treatment group were gastrointestinal disorders, infections and infestations, and nervous system disorders. A higher proportion of patients reported AEs within the SOC gastrointestinal disorders in the arimoclomol group compared with placebo. When considering the most frequently reported PTs within this SOC (vomiting, diarrhoea, and constipation), the proportion of patients reporting these PTs was similar between treatment groups. The incidence of TEAEs within the SOC nervous system disorders was slightly higher for arimoclomol than for placebo, while a slightly higher proportion of patients in the placebo group compared to arimoclomol group reported AEs within the SOC infections and infestations (Table 12-2).

Upon further investigation of the higher overall incidence of gastrointestinal events and nervous system disorders in the arimoclomol versus placebo groups, the higher incidence in the arimoclomol group appeared to be influenced by many reports of single or few events of individual PTs. In the nervous system disorders SOC, the TEAE reported by the highest proportion of patients in either treatment group was epilepsy with an incidence of 2.9% versus 18.8% in the arimoclomol versus placebo group. The remaining PTs reported by more than one patient was headache (8.8% versus 6.3%), lethargy (5.9% versus 0), seizure (8.8% versus 6.3%) and tremor (8.8% versus 0). Overall, the PTs showed similar occurrences across groups.

No other differences in the distribution of SOCs and PTs were apparent across treatment groups.

Table 12-2 TEAEs by SOC (>40%) and/or PT (>10%): Continuous Dose Period (Safety Set)

	Arimoclomol (N=34)		Placebo (N=16)		Total (N=50)	
	E	n (%)	E	n (%)	E	n (%)
Any Treatment Emergent Adverse Events	277	30 (88.2%)	92	13 (81.3%)	369	43 (86.0%)
Gastrointestinal disorders	75	21 (61.8%)	15	6 (37.5%)	90	27 (54.0%)
Constipation	14	7 (20.6%)	3	3 (18.8%)	17	10 (20.0%)
Diarrhoea	23	7 (20.6%)	4	3 (18.8%)	27	10 (20.0%)
Vomiting	26	8 (23.5%)	5	4 (25.0%)	31	12 (24.0%)
General disorders and administration site conditions	22	9 (26.5%)	5	4 (25.0%)	27	13 (26.0%)
Pyrexia	15	6 (17.6%)	4	3 (18.8%)	19	9 (18.0%)
Infections and infestations	50	23 (67.6%)	36	12 (75.0%)	86	35 (70.0%)
Bronchitis	5	4 (11.8%)	2	2 (12.5%)	7	6 (12.0%)
Ear infection	0	0	2	2 (12.5%)	2	2 (4.0%)
Eye infection	0	0	2	2 (12.5%)	2	2 (4.0%)
Gastroenteritis	2	2 (5.9%)	3	2 (12.5%)	5	4 (8.0%)
Nasopharyngitis	2	2 (5.9%)	4	4 (25.0%)	6	6 (12.0%)
Pneumonia	0	0	2	2 (12.5%)	2	2 (4.0%)
Respiratory tract infection	6	3 (8.8%)	3	2 (12.5%)	9	5 (10.0%)
Rhinitis	8	5 (14.7%)	5	2 (12.5%)	13	7 (14.0%)
Upper respiratory tract infection	8	6 (17.6%)	1	1 (6.3%)	9	7 (14.0%)
Investigations	20	8 (23.5%)	1	1 (6.3%)	21	9 (18.0%)
Weight decreased	6	5 (14.7%)	0	0	6	5 (10.0%)
Nervous system disorders	34	14 (41.2%)	13	4 (25.0%)	47	18 (36.0%)
Epilepsy	1	1 (2.9%)	5	3 (18.8%)	6	4 (8.0%)

The table presents number of events (E) and number and percentage of patients (n (%)).
The denominator for each percentage is the number of patients within the column.
Source: modified from [Table 14.3.2.1.2]

CT-ORZY-NPC-002 Open label Phase

The most frequently reported SOCs were Infections and infestations, Nervous system disorders, Gastrointestinal disorders, and Respiratory, thoracic, and mediastinal disorders.

Adverse events considered related to by the investigator

CT-ORZY-NPC-002 Double-blind Phase

A higher proportion of patients in the arimoclomol group than in the placebo group reported TEAEs assessed as IMP related by the investigator during the continuous dose period: 35.3% of the patients in the arimoclomol group and 18.8% of the patients in the placebo group. The most common TEAEs assessed as related to IMP was vomiting (reported by 14.7% in the arimoclomol group and none in the placebo group). The remaining TEAEs assessed as related to IMP were each reported by one or two patients in either group with no apparent clustering. None of the events were assessed as being related to the trial procedures. One event each of epilepsy and lethargy in the placebo group were assessed as related to the disease.

CT-ORZY-NPC-002 Open label Phase

The eight events assessed as at least possibly related to IMP were one event each of epilepsy, hypertonia, tremor, diarrhoea, abnormal blood creatinine level, increased blood triglyceride level, sleep disorder, and proteinuria. Of these, the one event of proteinuria was a serious TEAE.

Adverse events of special interest

CT-ORZY-NPC-002 Double-blind Phase

AEs within the SOC gastrointestinal disorders were predefined as AEs of special interest. One event of abdominal pain upper was reported in the single dose period. A higher proportion of patients in the arimoclomol group compared with the placebo group reported gastrointestinal events. A slightly higher proportion of patients reported AEs within the SOC gastrointestinal disorders in the arimoclomol group compared with placebo (61.8% versus 37.5%). However, when considering the most frequently reported PTs within this SOC (vomiting, diarrhoea, and constipation), the proportion of patients reporting these PTs was similar between treatment groups but the average number of events (E) per patient was higher in the arimoclomol group. Two gastrointestinal events were assessed as severe (an event of dysphagia in the arimoclomol group and an event of diarrhoea in the placebo group. There were no TEAEs of special interest ongoing into the continuous dose.

Table 2-24 **Treatment Emergent Adverse Events in Gastrointestinal Nonspecific Symptoms and Therapeutic Procedures (SMQ Narrow Scope) by PT - CT-ORZY-NPC-002 (Double-Blind Phase)**

	Arimoclomol 372 mg weight-adjusted N (%) E	Placebo N (%) E
Safety set (N,%)	34 (100.0)	16 (100.0)
Any treatment emergent adverse event	19 (55.9) 66	6 (37.5) 13
Vomiting	8 (23.5) 26	4 (25.0) 5
Diarrhoea	7 (20.6) 23	3 (18.8) 4
Constipation	7 (20.6) 14	3 (18.8) 3
Abdominal discomfort	1 (2.9) 1	
Abdominal distension	1 (2.9) 1	
Abdominal pain upper	1 (2.9) 1	
Nausea		1 (6.3) 1

N: Number of patients experiencing the event at least once, E: Total number of reportings of the event
PT: Preferred term, SMQ: Standardised MedDRA Queries
Coding Dictionary: MedDRA 19.0

CT-ORZY-NPC-002 Open label Phase

Table 1.25: Treatment Emergent Adverse Events - Gastrointestinal Nonspecific Symptoms and Therapeutic Procedures (SMQ Narrow Scope) by PT - CT-ORZY-NPC-002 (OL) - Safety Set

	Arimoclomol 372 mg weight-adjusted/ Arimoclomol 372 mg weight-adjusted N (%) E	Placebo/ Arimoclomol 372 mg weight-adjusted N (%) E	Arimoclomol Total N (%) E
Safety set (N,%)	26 (100.0)	15 (100.0)	41 (100.0)
Any treatment emergent adverse event	7 (26.9) 14	2 (13.3) 4	9 (22.0) 18
Diarrhoea	4 (15.4) 11	1 (6.7) 2	5 (12.2) 13
Vomiting	2 (7.7) 2	1 (6.7) 1	3 (7.3) 3
Constipation	1 (3.8) 1		1 (2.4) 1
Nausea		1 (6.7) 1	1 (2.4) 1

3.3.9.3. Serious adverse events, deaths, other significant events

Deaths

CT-ORZY-NPC-002 Double-blind + Open label Phase

As of 31 July 2020, very few patients have died in the CT-ORZY-NPC-002 trial. A total of 2 deaths have been reported in completed and ongoing trial phases in NPC. One patient died due to cardiorespiratory arrest in the DB phase and one patient due to lower respiratory tract infection in the OL phase. Both events were assessed as not related to IMP but rather related to the NPC disease

Other Indications

As of 31 July 2020, a total of 28 deaths have been reported in completed trials in other indications (all in ALS and ALS-SOD1). In line with the ALS disease where most common cause of death is respiratory failure the majority of fatal outcomes were due to respiratory failure. None of the events in the completed trials were assessed as related to IMP. Across trials, there was no indication of a higher rate of fatal events in the arimoclomol groups compared with placebo.

Serious Adverse Events

CT-ORZY-NPC-002 Double-blind Phase

Fewer patients reported treatment emergent SAEs in the arimoclomol group (14.7%) than in the placebo group (31.3%). Five out of 9 SAEs in the arimoclomol group and 5 out of 8 SAEs in placebo were severe. Out of these, one event (cardio-respiratory arrest), in the arimoclomol group, was fatal.

Most SAEs were single events and only two PTs were experienced by more than one patient in either treatment group (Urticaria was reported by 5.9% (2 patients) in the arimoclomol group and pneumonia was reported by 12.5 % (2 patients) in the placebo group). In both groups, the SAEs were mainly of the type that is expected in the NPC population.

Table 5-4 Treatment Emergent Serious Adverse Event by SOC and PT – CT-ORZY-NPC-002 (DB)

	Arimoclomol 372 mg weight-adjusted N (%) E	Placebo N (%) E
Safety set (N,%)	34 (100.0)	16 (100.0)
Any treatment emergent serious adverse event	5 (14.7) 9	5 (31.3) 8
Infections and infestations		3 (18.8) 3
Pneumonia		2 (12.5) 2
Lower respiratory tract infection		1 (6.3) 1
Skin and subcutaneous tissue disorders	2 (5.9) 3	
Urticaria	2 (5.9) 2	
Angioedema	1 (2.9) 1	
Gastrointestinal disorders	1 (2.9) 1	1 (6.3) 1
Diarrhoea		1 (6.3) 1

Dysphagia	1 (2.9) 1	
Metabolism and nutrition disorders	1 (2.9) 1	1 (6.3) 1
Hypophagia		1 (6.3) 1
Malnutrition	1 (2.9) 1	
Nervous system disorders	1 (2.9) 1	1 (6.3) 1
Epilepsy		1 (6.3) 1
Epileptic encephalopathy	1 (2.9) 1	
Cardiac disorders	1 (2.9) 1	
Cardio-respiratory arrest	1 (2.9) 1	
Injury, poisoning and procedural complications		1 (6.3) 1
Laceration		1 (6.3) 1
Investigations	1 (2.9) 1	
Aspiration bronchial	1 (2.9) 1	
Musculoskeletal and connective tissue disorders		1 (6.3) 1
Foot deformity		1 (6.3) 1
Respiratory, thoracic and mediastinal disorders	1 (2.9) 1	
Respiratory distress	1 (2.9) 1	

CT-ORZY-NPC-002 Open label Phase

One of the SAEs was fatal (an event of lower respiratory tract infection). Most events were single events and only 1 preferred term (epilepsy) was experienced by more than 1 patient. The SAEs were mainly of the type that is expected in the NPC population. Apart from the fatal event, 1 SAE (anaemia) led to withdrawal of IMP. One SAE (complete oral rehabilitation) led to interruption of IMP, and the remaining SAEs did not affect the IMP dosing. One event out of the 27 SAEs were assessed as probably related to arimoclomol (a moderate event of proteinuria that did not resolve but the arimoclomol dose continued unchanged). With the exception of the fatal SAE, 1 event each of dystonia and proteinuria, which did not resolve, and 1 event of urinary tract infection for which outcome was unknown, the remaining SAEs were all resolved.

3.3.9.4. Laboratory findings

Haematology

CT-ORZY-NPC-002 Double-blind Phase

Potentially Clinically Significant Abnormal Haematology Values

The overall incidences of patients with clinically significant haematology values were similar between the arimoclomol (8.8%) and the placebo (12.5%) groups.

Only a few patients had haematology values that reached the threshold for potential clinical significance (PCS) with no particular pattern in the parameters or values. Only one of these patients (which had PCS low levels of haemoglobin, platelets, erythrocytes and leukocytes) had an AE related to haematology parameters reported (thrombocytopenia).

CT-ORZY-NPC-002 Open label Phase

The following TEAEs associated with haematology parameters were reported in the extension phase (where all patients were on arimoclomol 372 mg weight-adjusted).

- One (mild) event of decreased platelet count (preferred term) assessed as not related to IMP. The event resolved, and the dose of IMP was not changed.
- Two (mild) events of thrombocytopenia (preferred term) in 2 patients, assessed as not related to IMP. The events did not resolve. The dose of IMP was not changed for either event.
- Two (severe) events of anaemia in 1 patient. The events were assessed as not related to IMP. The dose of IMP was not changed after the first event, but IMP was withdrawn after the second event. The patient had a history of epileptic seizures and high levels of erythrocytes at baseline.

No other TEAEs were reported for the haematology parameters

Potentially Clinically Significant Abnormal Haematology Values

Only a few patients had haematology values that were PCS with no particular pattern in the parameters or values. Two of the patients with PCS low platelet count had AEs reported: platelet count decreased with the PCS low platelet level and thrombocytopenia with the PCS low level. One of the patients with PCS high levels of erythrocytes (at baseline) had 2 severe events of anaemia (Section 3.1.3.1.2).

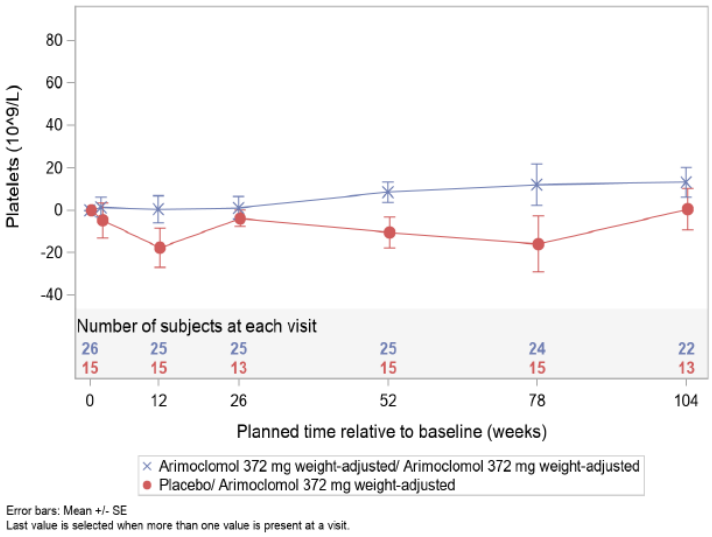
- Two patients had at least one PCS high level of eosinophils/leukocytes
- Three patients had at least one PCS low levels of platelets
- Two patients had at least one PCS high levels of erythrocytes

CT-ORZY-NPC-002 Double-blind+Open label Phase – long-term effect

The mean changes from baseline 1 (in the DB phase) during the two-year period were small and not clinically significant.

For platelets, the mean levels were stable (or slightly increased) over 2 years in the ari-ari patients whereas the mean platelet counts were fluctuating in the placebo-ari patients with indications of a slight increase after arimoclomol initiation (Figure 5-1).

Figure 5-1 **Mean Plot of Change from Baseline Platelets (10^9/L) - CT-ORZY-NPC-002 (Double-Blind + Open-Label Phase)**



Biochemistry

CT-ORZY-NPC-002 Double-blind Phase

The overall incidence of patients with clinically significant clinical chemistry values was higher in the arimoclomol group (11.8%) compared to the placebo group (6.3%).

The most commonly reported other clinical chemistry parameter reaching PCS levels was low levels of high-density lipoprotein (HDL) cholesterol (23.5% vs 25.0% in the arimoclomol and placebo group, respectively). Except for HDL cholesterol, the PCS values were in single patients with no pattern in type of parameter. There were no differences between the treatment groups:

CT-ORZY-NPC-002 Open label Phase

The most commonly reported parameter reaching the PCS levels was of low HDL cholesterol (29.3%). Except for high HDL cholesterol, the PCS values were in single patients with no particular pattern in type of parameter. The results were similar to the DB period.

Hepatic safety

CT-ORZY-NPC-002 Double-blind Phase

One patient in the arimoclomol group had fluctuating AST that was at ≥3xULN, with a temporary decrease to 2xULN in-between, after which the level decreased although the patient continued in the trial and the dose was not changed. The AST was already increased 2xULN at baseline. The increase was not accompanied by increased bilirubin or clinical symptoms.

None of the patients fulfilled Hy's law criteria (had increased transaminases in combination with increased bilirubin without evidence of cholestasis).

CT-ORZY-NPC-002 Open label Phase

No patients had transaminases above 3xULN and no patients fulfilled Hy's law criteria.

Other indications

AALS-001

One of the patients in arimoclomol 47 mg group had ALT ≥3xULN and 1 patient in the placebo group had ALT and AST ≥3xULN. The increases were not accompanied by increased bilirubin or clinical symptoms. For the arimoclomol patient the levels of ALT and AST fluctuated while treatment continued. None of the patients fulfilled Hy's law criteria.

AALS-001-OL

One patient reported ALT and AST≥3 x ULN during the OL trial. This patient also had ALT and AST ≥3 x ULN in the DB trial where the patient was treated with placebo. The maximum increases of ALT and AST did not occur at the same time and both parameters decreased over time. The patient did not have increased bilirubin or any accompanying clinical symptoms. The patient did not fulfil Hy's law criteria.

ALS SOD1

Two cases of ALT increased and AST increased (all in the placebo group) were reported.

IBM10656

In the arimoclomol group, one patient had increased AST at baseline and a slight increase up to ≥ 2 × ULN, after which the AST levels decreased, and another patient had bilirubin ≥ 1.5 × ULN at one visit during the trial, after which the levels decreased. In the placebo group, one patient had ALT ≥ 3× ULN and AST ≥ 2× ULN at baseline, after which the levels were at ≥ 2× ULN for both parameters over several visits before reaching normal limits at the post-treatment follow-up visit.

Renal Safety

CT-ORZY-NPC-002 Double-blind Phase

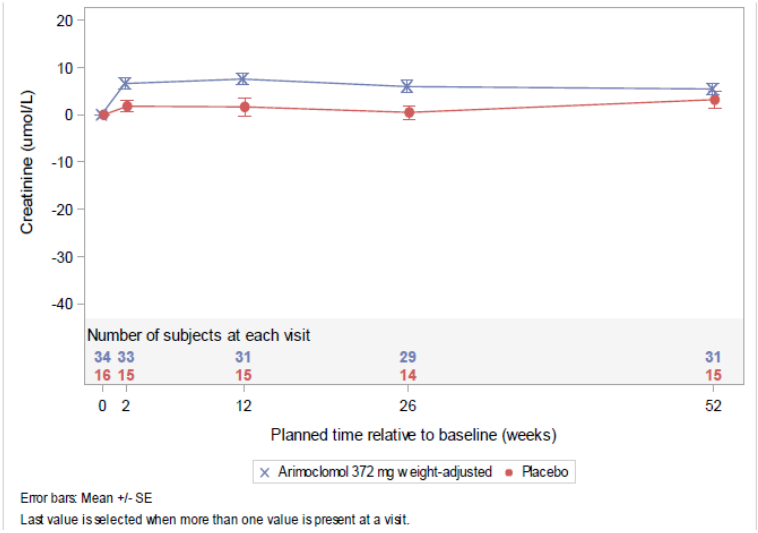
The mean levels of creatinine were similar at baseline in the two treatment groups. The mean creatinine level increased slightly in the arimoclomol group during the first 2 weeks of randomised treatment (approximately 16%) and remained stable for the remaining part of the 12 months treatment phase. In the placebo group, a smaller increase (3 %) was observed at Week 2. None of the patients had any clinical symptoms indicating affected renal function

Two events in the arimoclomol group

- one (moderate) event of blood creatinine increased relative to first randomised treatment assessed as probably related to IMP. The event resolved. The patient was withdrawn. The patient had creatinine ≥1.5x baseline value and creatinine ≥2.0x baseline value which had decreased below 1.5x baseline value. The patient had no clinical symptoms in relation to kidney function.
- one (mild) event of oliguria assessed as possibly related to IMP. The event resolved. The patient had no assessments of creatinine ≥1.5x baseline value.

No kidney-associated TEAEs were reported in the placebo group. There were no indications that increased creatinine was associated with decreased renal function.

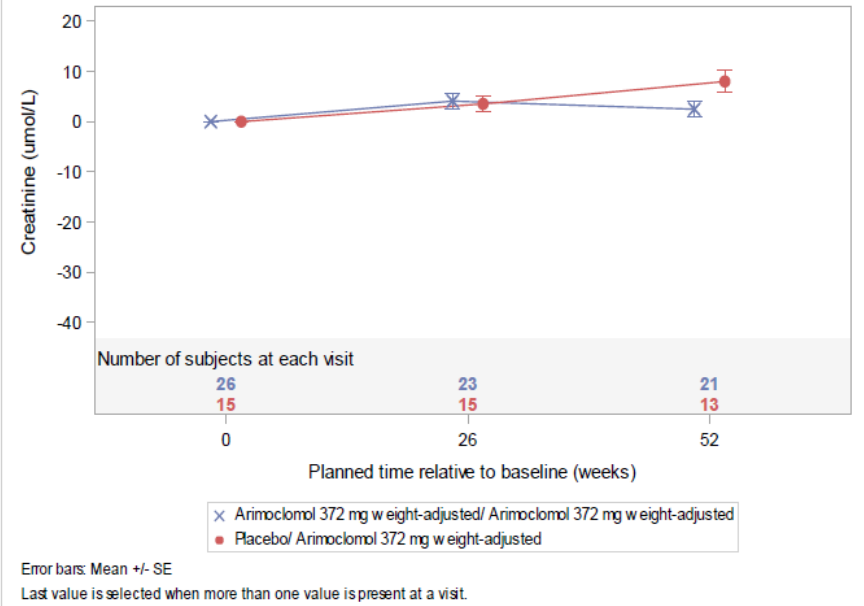
Figure 3-3 **Mean Plot of Change from Baseline (Double-Blind Phase) Creatinine (umol/L) - CT-ORZY-NPC-002**



CT-ORZY-NPC-002 Open-label Phase

The mean increase in serum creatinine level was higher in the former placebo patients (placebo-arimoclomol group) than in the arimoclomol-arimoclomol patients, when compared with Baseline 1 or Baseline 2. In fact, the mean creatinine level was stable in patients who continued to receive arimoclomol in the open-label phase (arimoclomol-arimoclomol group); however, it increased in the former placebo patients (placebo-arimoclomol group) to a level similar to the arimoclomol-arimoclomol patients. Three patients (2 in the arimoclomol-arimoclomol group and 1 in the placebo-arimoclomol group) had an increase in serum creatinine level that was above 1.5 times the patient's own Baseline 2 value Individual blood urea nitrogen, potassium, and sodium levels did not correlate with the increase in creatinine. The change from Baseline and Baseline 2 in the mean level of blood urea nitrogen was small and not clinically significant. None of the patients had any clinical symptoms indicating renal failure.

Figure 3-5 **Mean Plot of Change from Baseline (Open-Label Phase) Creatinine (µmol/L) - CT-ORZY-NPC-002 (Open-Label Phase)**



Three patients reported the below TEAEs of kidney related findings in the SOC Investigations, Renal and Urinary Disorders or Metabolism and Nutrition Disorders in the OL trial:

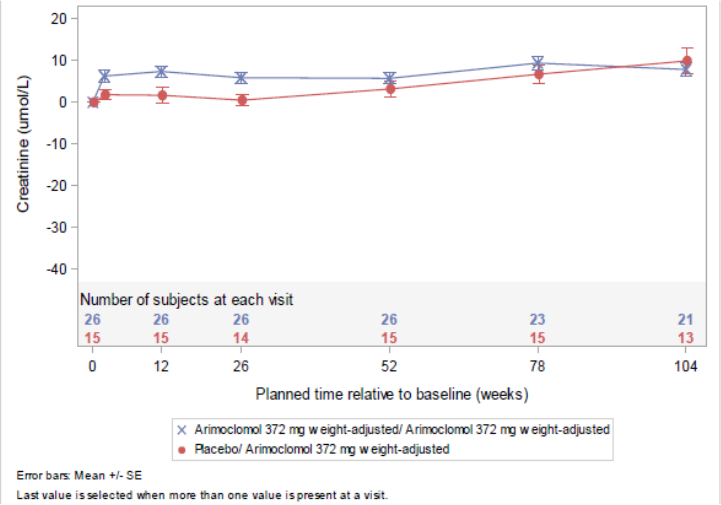
- one (mild) event of blood creatinine abnormal assessed as probably related to IMP. IMP was interrupted. Outcome unknown. The patient had creatinine ≥1.5x baseline value.
- one (mild) event of hypokalaemia, assessed as not related. The event did not resolve and the dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- one (moderate) event of proteinuria, assessed as probably related to IMP. The event did not resolve. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

<u>CT-ORZY-NPC-002 Double-blind + Open label Phase</u>

The mean levels of creatinine were similar at Baseline 1 in the two treatment groups. The mean level of creatinine increased over the DB phase for patients in the arimoclomol group after which the level stabilised in the OL extension phase (Figure 5-2).

The mean levels of BUN were similar across groups at Baseline 1 and the change from baseline was small and not clinically significant in the ari-ari patients.

Figure 5-2 **Mean Plot of Change from Baseline Creatinine (µmol/L) - CT-ORZY-NPC-002 (Double-Blind + Open-Label Phase)**



Other indications

AALS-001

The mean level of creatinine was slightly higher in the placebo group than in the arimoclomol groups at baseline. The mean creatinine level increased slightly in the arimoclomol groups during the first 2 weeks of treatment (approximately 6-11% across groups) and remained stable for remaining part of the 12-week treatment period. However, there was no indication of a dose-response. In the placebo group, no increase was observed.

Table 3-9 **Proportion of Patients with a Creatinine Clearance Decrease of 50% or more from Screening– AALS-001**

	Arimoclomol 47 mg	Arimoclomol 93 mg	Arimoclomol 186 mg	Arimoclomol Total	Placebo
Decreased Creatinine clearance at Week 12	37% (7/19)	30% (6/20)	43% (9/21)	37% (22/60)	18% (4/22)
Decreased Creatinine clearance at Week 16	0 (0/17)	5% (1/19)	6% (1/17)	4% (2/53)	5 (1/20)

% (# patients with events/# patients in dose group)
Source: [AALS-001, Table 12.4.2-1 and 12.4.2-3]

In the arimoclomol 47 mg dose group

- Three (mild) events (in two patients) of creatinine renal clearance decreased). All events assessed as possibly related to IMP. Outcome unknown. The dose was not changed. The patients had no assessments of creatinine ≥1.5x baseline value.
- One (mild) event of proteinuria. The event was assessed as possibly related to IMP. Outcome unknown. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

In the arimoclomol 93 mg dose group

- Four (1 mild, 2 moderate and 1 severe) events (in 4 patients) of creatinine renal clearance decreased. All events were assessed as possibly or probably related to IMP. Outcomes were unknown. The dose was not changed for the mild event but dosing was interrupted for the

moderate and severe events. The patients had no assessments of creatinine ≥1.5x baseline value.

- One (moderate) event of white blood cells urine positive, assessed as not related to IMP. Outcome unknown. The dose was not changed. The patient had no assessments of creatinine ≥ 1.5x baseline value.

In the arimoclomol 186 mg dose group

- One mild event of creatinine renal clearance decreased, assessed as probably related to IMP. Outcome unknown. The dose was interrupted. The patient had creatinine ≥1.5x baseline value. The level had decreased below 1.5x baseline at the post treatment visit.
- One (mild) event of blood potassium decreased, assessed as not related to IMP and one (moderate) event of creatinine renal clearance decreased, assessed as possibly related to IMP in 1 patient. Outcomes were unknown. The dose was interrupted for the event of creatinine renal clearance decreased. The patient had creatinine ≥1.5x baseline value after which the level decreased below 1.5x baseline value.
- One event each (all mild) of urine odour abnormal, urine output decreased and micturition frequency decreased in 1 patient. All events assessed as possibly related to IMP. Outcomes unknown. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

In the placebo group

- One event each (both moderate) of creatinine renal clearance decreased and blood creatinine increased in 1 patient for both. Both events assessed as probably related to IMP. Outcomes were unknown. The dose (of placebo) was reduced. The patient had no assessments of creatinine ≥1.5x baseline value.
- One event each (both mild) of albumin urine present and proteinuria in 1 patient; both events were assessed as possibly related to IMP. Outcomes were unknown for both events. IMP was withdrawn for the event of proteinuria. The patient had no assessments of creatinine ≥1.5x baseline value.

<u>AALS-001-OL</u>

Five patients had an increase in creatinine that was above 1.5 times the patients' own baseline values during the trial (one of these patients had also reported high levels in the DB trial); none were above 2 times. The maximum creatinine level was observed between 1 and 5 months into the trial. Individual urea nitrogen, potassium and sodium levels did not correlate with the increase in creatinine

- One mild event of blood creatinine increased and one (mild) event of blood urea increased in 1 patient for both events. Both events were assessed as possibly related to IMP. The events resolved. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- One mild event each of blood urine present, hypokalaemia and alkalosis hypochloraemia in 1 patient. All events were assessed as not related to IMP. The event of hypokalaemia resolved; the other events did not resolve. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- One event each (both mild) of hypokalaemia and urinary retention in 1 patient. Both were assessed as not related to IMP. The event of hypokalaemia resolved; the other event did not

resolve. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

ALS SOD1

The mean levels of creatinine at baseline were slightly higher in the arimoclomol group than in the placebo group. After an initial increase in mean creatinine after 1 month in the arimoclomol group, the creatinine levels showed a similar decline across groups during the remaining part of the trial. This decline is in line with what can be expected for ALS patients when loosing muscle mass (especially in this aggressive form of ALS). It should be noted that the number of patients in both groups also declined markedly during the trial.

In the arimoclomol 372 mg dose group

- One moderate event of blood urea decreased assessed as not related to IMP. Outcome unknown. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- One severe event of blood urea increased assessed as not related to IMP. Outcome unknown. The dose was not changed. One severe event of incontinence assessed as not related to IMP. The event resolved with sequelae. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- One mild event of urine abnormality assessed as not related to IMP. The event resolved. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

In the placebo group

- One (mild) event of hypokalaemia assessed as not related to IMP. The event did not resolve. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.
- One (mild) event of renal pain assessed as not related to IMP. The event resolved. The dose was not changed. The patient had no assessments of creatinine ≥1.5x baseline value.

IBM10656

In the arimoclomol group:

- one (mild) events of hyponatraemia. The event was assessed as possibly related to IMP. The event resolved. Dose impact is unknown. The patient had no assessments of creatinine ≥1.5x baseline value.
- two (moderate) events (one each of hyponatraemia and haemorrhage urinary tract in 1 patient. The event of hyponatraemia was assessed possibly relayed to IMP; the other event as not related to IMP. The events resolved. The dose was not changed for the hyponatraemia but interrupted due to the event of haemorrhage. The patient had no assessments of creatinine ≥ 1.5x baseline value.

No kidney-related findings were reported in the placebo group.

Vital signs, physical findings, and other observations related to safety

CT-ORZY-NPC-002 Double-blind Phase

Overall, the mean values were similar across groups during the DB phase and the mean changes from baseline were small and not clinically significant.

Table 4-3 **Change in Body Weight (kg) - Patients with a Change in Weight of ≥ 7% from Baseline during the Trial - CT- ORZY-NPC-002 (Double-Blind Phase)**

	Arimoclomol 372 mg weight-adjusted N (%)	Placebo N (%)
Safety set (N,%)	34 (100.0)	16 (100.0)
Decrease ≥ 7%	8 (23.5)	2 (12.5)
Increase ≥ 7%	15 (44.1)	11 (68.8)

N: Number of patients

	NPC-002 (DB)		Other Indications	
	Arimoclomol 372 mg weight-adjusted N (%)	Placebo N (%)	Arimoclomol 46.5-372 mg N (%)	Placebo N (%)
Safety set (N,%)	34 (100.0)	16 (100.0)	97 (100.0)	49 (100.0)
Systolic Blood Pressure (mmHg)				
Value <= 90 and change <= -20	2 (5.9)	0 (0.0)	3 (3.1)	0 (0.0)
Value > 180 and change >= 20	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)
Diastolic Blood Pressure (mmHg)				
Value <= 50 and change <= -15	4 (11.8)	0 (0.0)	1 (1.0)	0 (0.0)
Value > 105 and change >= 15	1 (2.9)	0 (0.0)	1 (1.0)	1 (2.0)
Pulse Rate (beats/min)				
Value < 50 and change <= -15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Value > 120 and change >= 15	6 (17.6)	1 (6.3)	0 (0.0)	0 (0.0)

CT-ORZY-NPC-002 Open label Phase

Table 4-4 **Patients with a Change in Weight of ≥ 7% from Baseline during the Trial - CT-ORZY-NPC-002 (Open-Label)**

	Arimoclomol 372 mg weight-adjusted/ Arimoclomol 372 mg weight-adjusted N(%)	Placebo/ Arimoclomol 372 mg weight-adjusted N(%)	Arimoclomol Total N(%)
Safety set (N,%)	26 (100.0)	15 (100.0)	41 (100.0)
Decrease ≥ 7%	2 (7.7)	0 (0)	2 (4.9)
Increase ≥ 7%	9 (34.6)	9 (60.0)	18 (43.9)

N: Number of patients

Other indications

AALS-001 / ALS SOD1 / IBM10656

Overall, the mean values were similar across groups at baseline and the mean changes from baseline were small and not clinically significant.

Electrocardiograms

Pharmacology studies

Table 1.41: Summary of ECG - Multiple Dose - Safety Set (Continued)

	Arimoclomol 93 mg	Arimoclomol 186 mg	Arimoclomol 372 mg	Arimoclomol 744 mg	Arimoclomol 1116 mg	Arimoclomol Total	Placebo
Interpretation							
Baseline							
Abnormal				2 (8.0)		2 (3.4)	
Abnormal, not clinically significant		3 (23.1)	2 (28.6)	10 (40.0)	4 (57.1)	19 (32.8)	8 (36.4)
Normal	6 (100.0)	10 (76.9)	5 (71.4)	13 (52.0)	3 (42.9)	37 (63.8)	14 (63.6)
Total	6 (100.0)	13 (100.0)	7 (100.0)	25 (100.0)	7 (100.0)	58 (100.0)	22 (100.0)
Last Visit (MD)							
Abnormal				3 (12.0)		3 (5.2)	
Abnormal, not clinically significant		3 (23.1)	3 (42.9)	12 (48.0)	5 (71.4)	23 (39.7)	4 (18.2)
Normal	6 (100.0)	10 (76.9)	4 (57.1)	10 (40.0)	2 (28.6)	32 (55.2)	18 (81.8)
Total	6 (100.0)	13 (100.0)	7 (100.0)	25 (100.0)	7 (100.0)	58 (100.0)	22 (100.0)

CT-ORZY-NPC-002 Double-blind + Open label Phase

The majority of patients in both groups were assessed to have normal ECG readings at baseline and throughout the trial. No abnormal clinically significant findings were recorded. A few patients were assessed to have abnormal, not clinically significant ECGs at baseline and during the trial. No major changes were noted during the DB phase.

Table 1.41: Summary of ECG - CT-ORZY-NPC-002 (DB) - Safety Set

	Arimoclomol 372 mg weight-adjusted	Placebo
Safety set (N,%)	34 (100.0)	16 (100.0)
Interpretation		
Baseline		
Abnormal, not clinically significant	3 (8.8)	1 (6.3)
Normal	31 (91.2)	15 (93.8)
Total	34 (100.0)	16 (100.0)
Visit 4		
Abnormal, not clinically significant	3 (8.8)	1 (6.3)
Normal	25 (73.5)	14 (87.5)
Total	28 (82.4)	15 (93.8)
Visit 6/End of BP		
Abnormal, not clinically significant	4 (11.8)	1 (6.3)
Normal	26 (76.5)	14 (87.5)
Total	30 (88.2)	15 (93.8)

Other Indications

AALS-001

- One (mild) event of tachycardia was reported (in a patient in the arimoclomol 186 mg dose group). The event was assessed as not related to IMP. Outcome unknown. The dose was not changed

AALS-001-OL

Two events were reported in the OL trial

- One (moderate) event of electrocardiogram T wave abnormal assessed as possibly related to IMP. The event did not resolve. The dose was not changed.

- One (moderate) event of heart rate decreased assessed as not related to IMP. The event resolved. The dose was not changed.

ALS-SOD1

- One patient in the placebo group reported a (severe) event of tachycardia assessed as possibly related to IMP. The event resolved. The dose was not changed.

IBM10656

- One (mild) event of cardiac flutter was reported in a patient in the arimoclomol group in the in-trial period assessed as not related to IMP. The event was resolved. The dose was not changed.

3.3.9.5. Safety in special populations

Gender

Table 5-9 Gender Distribution – CT-ORZY-NPC-002 (Double-Blind Phase)

	Arimoclomol 372 mg weight-adjusted N	Placebo N
Female	17	9
Male	17	7

N: Number of patients.
Source: [M5.3.5.3 NPC002 Tables 1.18.1, 1.18.2,]

Ethnicity

The population studied in the pivotal study CT- ORZY-NPC-002 was predominantly white (94.1% - arimoclomol and 81.3% - placebo).

Age category (paediatric and elderly patients)

Table 5-1 Baseline Age Group Distribution – CT-ORZY-NPC-002 (Double-blind Phase)

	Arimoclomol 372 mg weight-adjusted	Placebo
Age < 4 Years	4	2
4 Years ≤ Age < 12 Years	12	9
12 Years ≤ Age < 18 Years	13	5
18 Years ≤ Age < 19 Years	5	-

N: Number of patients.

MedDRA Terms	**Age <65** **number (percentage)**	**Age 65-74** **number (percentage)**	**Age 75-84** **number (percentage)**	**Age 85+** **number (percentage)**

The applicant should provide this table as part of the answers to the day 120 LoQ.

3.3.9.6. Immunological events

Not applicable.

3.3.9.7. Safety related to drug-drug interactions and other interactions

Results from an *in vitro* transporter study assessing the interaction of arimoclomol with the human solute carrier uptake transporters indicate that arimoclomol is an inhibitor of the OCT2 transporter. Arimoclomol may therefore inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an *in vitro* substrate of the MATE-1 and MATE-2K transporters and undergoes active renal secretion.

The clinical significance is considered low due to the low likeliness of concomitant use of MATE inhibitors in the NPC population and since arimoclomol is not considered to be a narrow-therapeutic-index drug.

3.3.9.8. Discontinuation due to adverse events

CT-ORZY-NPC-002 Double-blind Phase

Four events in three patients in the arimoclomol group and no events in the placebo group led to withdrawal from IMP. The events were two events of urticaria and one event each of angioedema and blood creatinine increased. The four events were assessed as probably or possibly related to IMP.

CT-ORZY-NPC-002 Open label Phase

Five events (1 fatal) in three patients led to withdrawal from IMP. The events were all in line with progression of NPC, but two events (hypertonia and tremor) were assessed as possibly related to IMP.

- one patient had a moderate event each of muscular hypertonia and tremor. The patient recovered. The events were assessed as possibly related to IMP.
- one patient had a severe and serious event of anaemia starting (anaemia was resolved). The events were assessed as not related to IMP.
- one patient had a severe (fatal) event of lower respiratory tract infection. The event was assessed as not related to IMP.

3.3.9.9. Post marketing experience

Not applicable.

3.3.9.10. Additional data provided in D120 responses

The Applicant provided the results of the recently completed TQT trial (OR-ARI-TQT-01 trial) showing that arimoclomol did not have a clinically relevant effect on heart rate or on cardiac conduction i.e., the PR and QRS intervals. The applicant further provided data that only few AEs were observed in the studies using the SMQ Torsade de pointes/QT prolongation (broad scope) and SMQ Myocardial infarction search terms.

OR-ARI-TQT-01: Interventional, randomised, partial double-blind, placebo- and positive- controlled, multiple-dose, 4-way crossover trial investigating the effect of arimoclomol on cardiac repolarisation in healthy men

34 healthy men were enrolled, and 33 men completed this 12-sequence, 4-period trial where the subjects received multiple doses of 124 mg arimoclomol (372 mg/day; therapeutic dose), 372 mg arimoclomol (1116 mg/day; supratherapeutic dose), placebo, and a single dose of 400 mg moxifloxacin. Subjects received arimoclomol 3 times on Day 1 and 2 and a single dose in the morning on Day 3. Each treatment period was separated by a washout period of at least 17 days. Digital, triplicate, 12-lead electrocardiograms (ECGs) were extracted from a continuous Holter recordings for

QTc assessments pre-dose (-45, -30 and -15 minutes) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours post morning dose on Day 1, and pre-dose (-15 minutes) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dosing on Day 3 in each dosing period. Blood samples for determination of arimoclomol and its most abundant metabolites M2 and M105 in plasma were collected at the same time points.

Primary endpoint
• Placebo-corrected change-from-baseline QTcF (ΔΔQTcF)

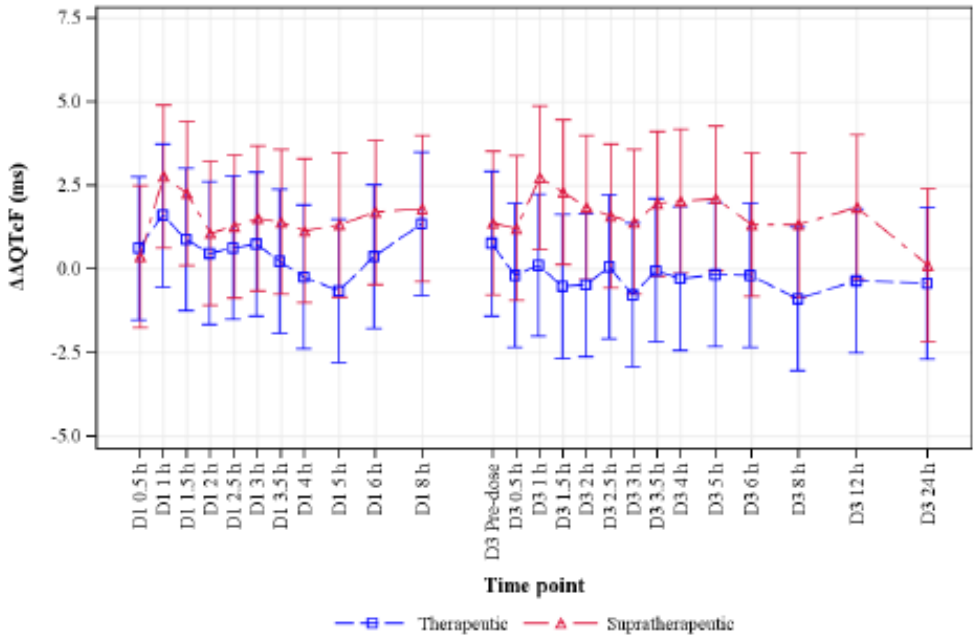
Secondary endpoints
• Change-from-baseline QTcF, HR, PR, QRS intervals (ΔQTcF, ΔHR, ΔPR, and ΔQRS)
• Placebo-corrected change-from-baseline HR, PR, and QRS (ΔΔHR, ΔΔPR, ΔΔQRS)
• Categorical outliers for QTcF, HR, PR, and QRS
• Frequency of treatment-emergent changes of T-wave morphology and U-waves presence

Safety endpoints
• AEs
• Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, and safety ECG parameter values
• Clinically significant clinical safety laboratory test values, vital signs, and safety ECG parameter values

Pharmacokinetic endpoints for arimoclomol, M2 and M105

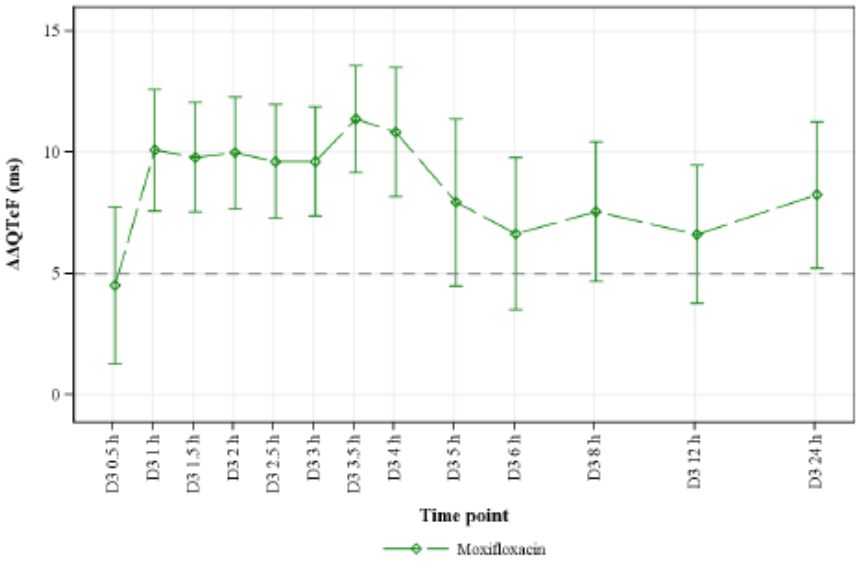
Results:

Figure 14.2.3.1 Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) across time points (QT/QTc population)



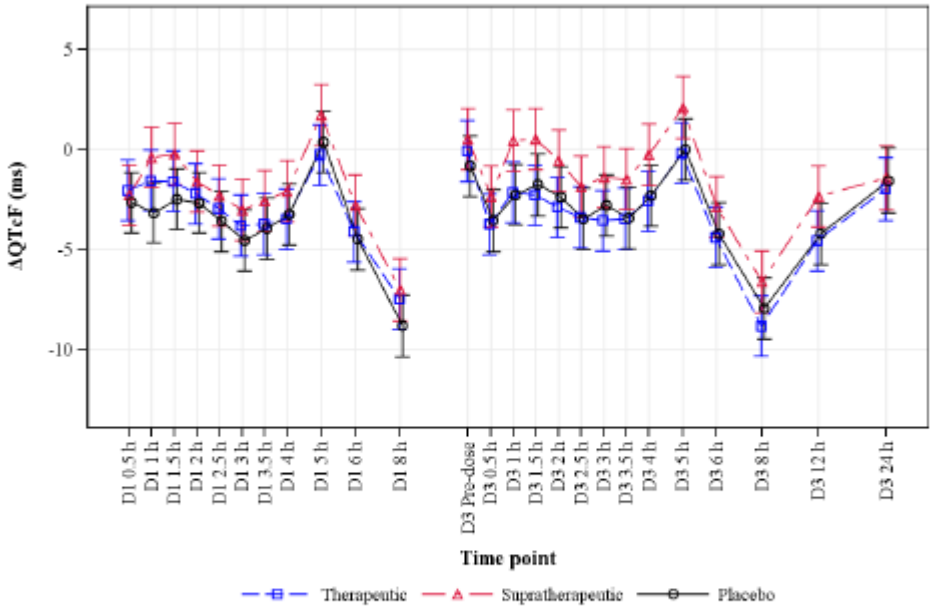
LS Mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF + Sequence + Period. A compound symmetry covariance structure was used to specify the repeated measures (at post-baseline time points for subject within treatment period). A random intercept per subject with an unstructured covariance structure.

Figure 14.2.3.5 Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) across time points for moxifloxacin (QT/QTc population)



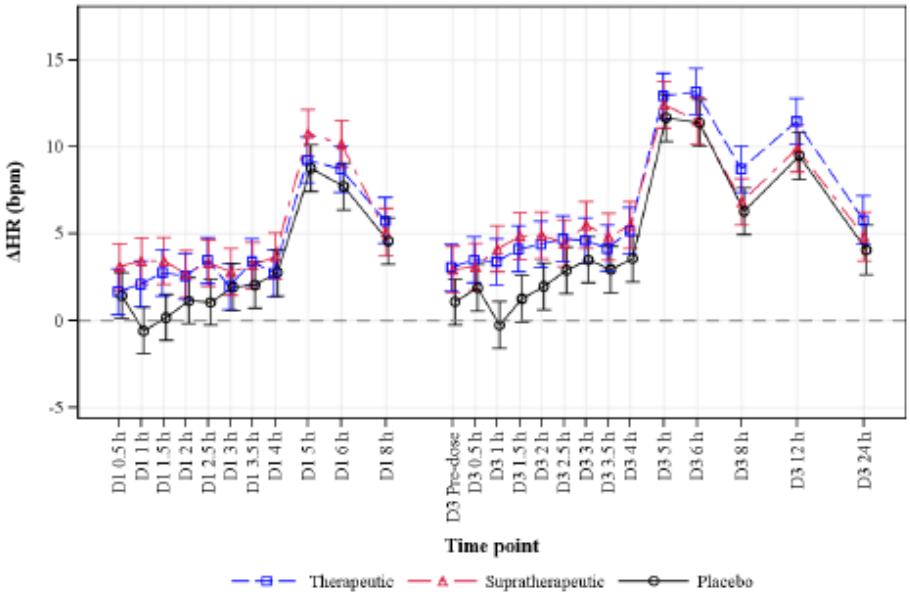
LS Mean and 90% CI based on a linear mixed-effects model for moxifloxacin and placebo treatment groups: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF + Sequence + Period. An unstructured covariance structure was used to specify the repeated measures (at post-baseline time points for subject within treatment period).

Figure 14.2.2.1 Change-from-baseline QTcF (ΔQTcF) across time points (QT/QTc population)



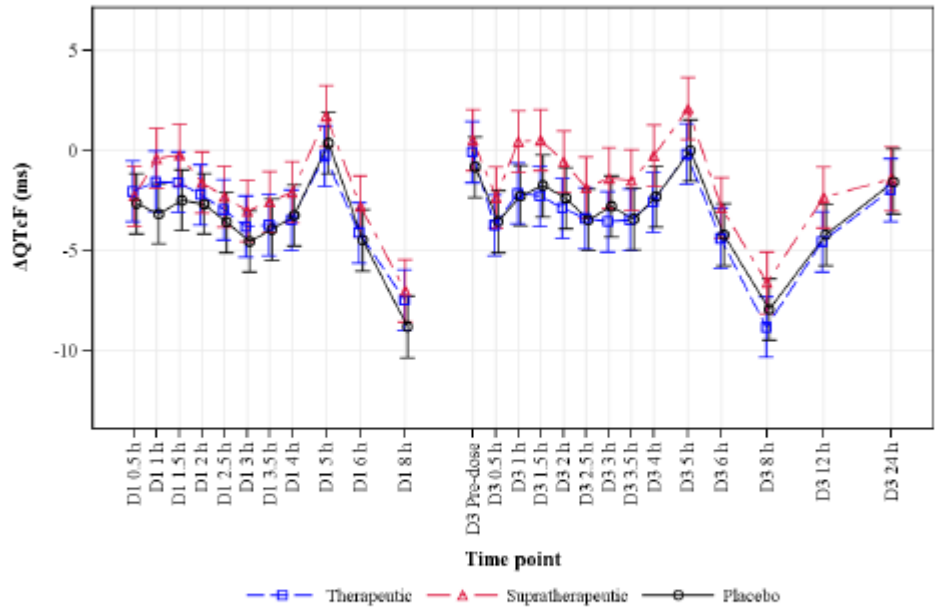
LS Mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF + Sequence + Period. A compound symmetry covariance structure was used to specify the repeated measures (at post-baseline time points for subject within treatment period). A random intercept per subject with an unstructured covariance structure.

Figure 14.2.2.2 Change-from-baseline HR (ΔHR) across time points (QT/QTc population)



LS Mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔHR = Time + Treatment + Time×Treatment + Baseline HR + Sequence + Period. A compound symmetry covariance structure was used to specify the repeated measures (at post-baseline time points for subject within treatment period). A random intercept per subject with an unstructured covariance structure.

Figure 14.2.2.1 Change-from-baseline QTcF (ΔQTcF) across time points (QT/QTc population)



LS Mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF + Sequence + Period. A compound symmetry covariance structure was used to specify the repeated measures (at post-baseline time points for subject within treatment period). A random intercept per subject with an unstructured covariance structure.

In the by-time point analysis, mean change-from-baseline QTcF (ΔQTcF) on arimoclomol closely followed the placebo pattern across post-dose time points. Mean placebo-corrected ΔQTcF (ΔΔQTcF) across post-baseline time points on Days 1 and 3 ranged from −0.9 ms (on Day 3 at 8 hours post-dose

on the therapeutic dose) to 2.8 ms (on Day 1 at 1 hour post-dose on the supratherapeutic dose). After dosing with 400 mg oral moxifloxacin, a clear increase of mean ΔΔQTcF was observed with a peak value of 11.4 ms (90% CI: 9.17 to 13.59) at 3.5 hours post-dose.

Arimoclomol at the studied doses did not have a clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals, or on HR.

For the therapeutic dose of arimoclomol, the effect on ΔΔQTcF can be predicted to 0.42 ms (90% CI: 0.00 to 0.84) at an overall geometric mean Cmax of 1478.7 ng/mL. For the supratherapeutic dose of arimoclomol, the effect on ΔΔQTcF can be predicted to 2.18 ms (90%CI: 1.01 to 3.34) at an overall geometric mean Cmax of 4823.5 ng/mL. Based on this concentration-QTc analysis, a QTcF effect (ΔΔQTcF) exceeding 10 ms can be excluded up to arimoclomol citrate plasma concentrations of ~6900 ng/mL. These results constitute a negative TQT study, as described in the ICH E14 clinical guidance document.

Adverse events:

• No treatment-emergent SAEs (TESAEs) were reported after any of the treatments.

• There were no deaths or other serious or significant AEs.

• Overall, 21 subjects (61.76%) reported a total of 55 TEAEs.

• Most of the TEAEs (21 events by 11 subjects) were reported after Treatment A (therapeutic dose arimoclomol), followed by Treatment B (supratherapeutic dose arimoclomol) (14 events by 10 subjects), Treatment D (moxifloxacin) (12 events by 9 subjects), and Treatment C (placebo) (8 events by 7 subjects).

• No TEAEs of severe intensity were reported.

• One (1) subject reported 1 moderate TEAE (root canal infection). This TEAE was not related to IMP (therapeutic dose arimoclomol). All other TEAEs were of mild intensity.

• One (1) subject reported 1 TEAE (headache) that was considered probably related to IMP (therapeutic dose arimoclomol), and 12 subjects reported 25 TEAEs that were considered possibly related to the IMP.

• Headache was the most frequently reported related TEAE considered related to treatment. Headache considered related to treatment was reported after Treatment A (therapeutic dose arimoclomol) (2 subjects, 3 events), Treatment B (supratherapeutic dose arimoclomol) (2 subjects, 2 events), and Treatment C (placebo) (2 subjects, 2 events).

• One (1) subject reported 1 TEAE (ear discomfort) which was not recovered. This TEAE was not related to IMP (moxifloxacin). All other TEAEs recovered.

• None of the laboratory parameters or vital sign parameters showed any treatment- or time-related effect.

• There were no treatment- or time-dependent changes in any of the safety ECG parameters observed.

• One (1) clinically significant abnormality was reported in the physical examination; a left inguinal hernia for. This abnormality was documented as a mild, not related TEAE.

• No clinically significant abnormalities were reported for any of the neurological parameters.

• One (1) subject reported suicidal ideation. Subject did not have active suicidal ideations and was subsequently dosed with the IMPs. No other suicidal ideations or behaviors were reported for this subject or any of the other subjects.

3.3.9.11. Additional data provided in D180 responses

The applicant provided results of the recently completed **renal safety study (OR-ARI-REN-01)**

Interventional, open-label, four-group, **single-dose** trial investigating the pharmacokinetic properties of arimoclomol in subjects with mild, moderate and severe renal impairment and normal renal function. It was planned to include 32 male and female subjects. Eight subjects were planned to be included in each of the 4 following groups depending on their renal function:

• Group 1: Mild renal impairment

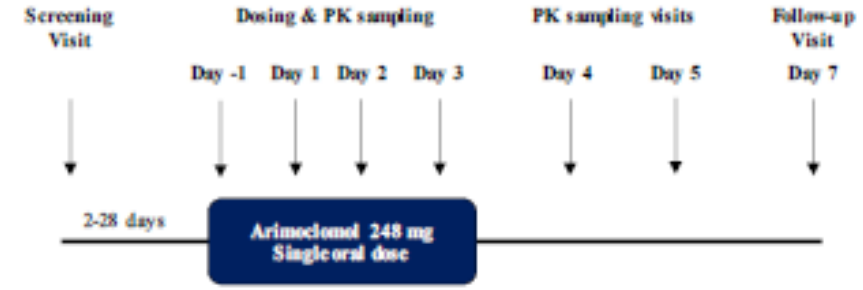
• Group 2: Moderate renal impairment

• Group 3: Severe renal impairment

• Group 4: Normal renal function

The trial included a screening visit (Days -28 to -2); a baseline visit (Day -1); a trial period that included dosing and PK sampling on Days 1 to 3, two PK sampling visits on Days 4 and 5; and a follow-up visit on Day 7 (Figure 1). Subjects were confined at the trial site from Day -1 to Day 3 and returned to the site for 2 PK sampling visits and a follow-up visit. The total trial duration per subject from the baseline visit to the follow-up visit on Day 7 was between 8 to 10 days.

Figure 1: Visit Schedule



Trial rationale:

The trial described in this report is part of the clinical development programme for arimoclomol. The trial investigated the PK properties of arimoclomol in subjects with renal impairment. Because >40% of the arimoclomol dose is excreted unchanged in the urine, there is a potential risk of renal impairment altering systemic exposure of arimoclomol. The rationale for this trial was to assess whether dose adjustment of arimoclomol was needed for subjects with impaired renal function.

Objectives:

The **primary objective** was to investigate the impact of renal impairment (mild, moderate, severe) on the PK of a single oral dose of arimoclomol.

The **secondary objective** was to investigate the safety and tolerability of arimoclomol after a single oral dose in subjects with renal impairment.

The **exploratory objective** was to explore the impact of renal impairment on the PK of the M2 and M105 metabolites of arimoclomol.

Endpoints:

The primary PK endpoints were:
• area under the concentration-time curve from time 0 to infinity (AUC0-inf)
• Cmax.
The secondary PK endpoints were:
• area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC0-t)
• tmax
• t1/2
• apparent total clearance (CL/F)
• apparent total volume of distribution (Vz/F).

The secondary safety endpoints were:
• AEs
• neurological examination
• vital signs • electrocardiogram (ECG)
• clinical safety laboratory parameters.

The exploratory PK endpoints for metabolites M2 and M105 were:
• AUC0-inf
• AUC0-t
• Cmax
• metabolic ratio (MR)
• t1/2.

Results

PK (Single Oral Dose Pharmacokinetics of Arimoclomol Citrate – Primary endpoint):

Table 8: Summary of the Arimoclomol Citrate Pharmacokinetic Parameters

Matrix: Plasma; Analyte: Arimoclomol Citrate; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Mild renal impairment (N = 8)	Moderate renal impairment (N = 8)	Severe renal impairment (N = 6)	Normal renal function (N = 8)
$AUC_{0\text{-}8h}$ (h*ng/mL)	9690 (15.4) [8]	9760 (16.9) [8]	13600 (17.1) [6]	8570 (17.0) [8]
$AUC_{0\text{-}t}$ (h*ng/mL)	12200 (17.1) [8]	14700 (26.5) [8]	26500 (24.6) [6]	11200 (17.3) [8]
$AUC_{0\text{-}inf}$ (h*ng/mL)	12300 (17.3) [8]	15100 (25.7) [8]	26800 (24.3) [6]	11400 (17.5) [8]
t_{max} (h)	0.75 (0.50-1.50) [8]	1.50 (1.50-3.00) [8]	2.01 (1.00-3.03) [6]	1.25 (0.50-2.00) [8]
C_{max} (ng/mL)	3050 (22.6) [8]	2210 (21.7) [8]	2540 (13.3) [6]	2240 (26.4) [8]
$t_{1/2}$ (h)	3.76 (4.7) [8]	5.05 (30.7) [8]	9.36 (12.5) [6]	4.31 (7.2) [8]
CL/F (L/h)	32.4 (17.3) [8]	26.4 (25.7) [8]	14.9 (24.3) [6]	35.2 (17.5) [8]
V_z/F (L)	176 (15.4) [8]	193 (12.8) [8]	202 (23.1) [6]	219 (15.1) [8]

Table 9: Statistical Analysis of Arimoclomol Citrate Pharmacokinetic Parameters

Matrix: Plasma; Analyte: Arimoclomol Citrate; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Renal Function Group	n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)
$AUC_{0\text{-}inf}$ (h*ng/mL)	Normal renal function (Reference)	8	11000	
	Mild renal impairment (Test)	8	12100	1.0949 (0.9213, 1.3011)
	Moderate renal impairment (Test)	8	15400	1.4010 (1.1611, 1.6903)
	Severe renal impairment (Test)	6	26700	2.4189 (2.0281, 2.8850)
C_{max} (ng/mL)	Normal renal function (Reference)	8	2250	
	Mild renal impairment (Test)	8	3030	1.3435 (1.0887, 1.6579)
	Moderate renal impairment (Test)	8	2240	0.9929 (0.7899, 1.2482)
	Severe renal impairment (Test)	6	2560	1.1378 (0.9180, 1.4103)

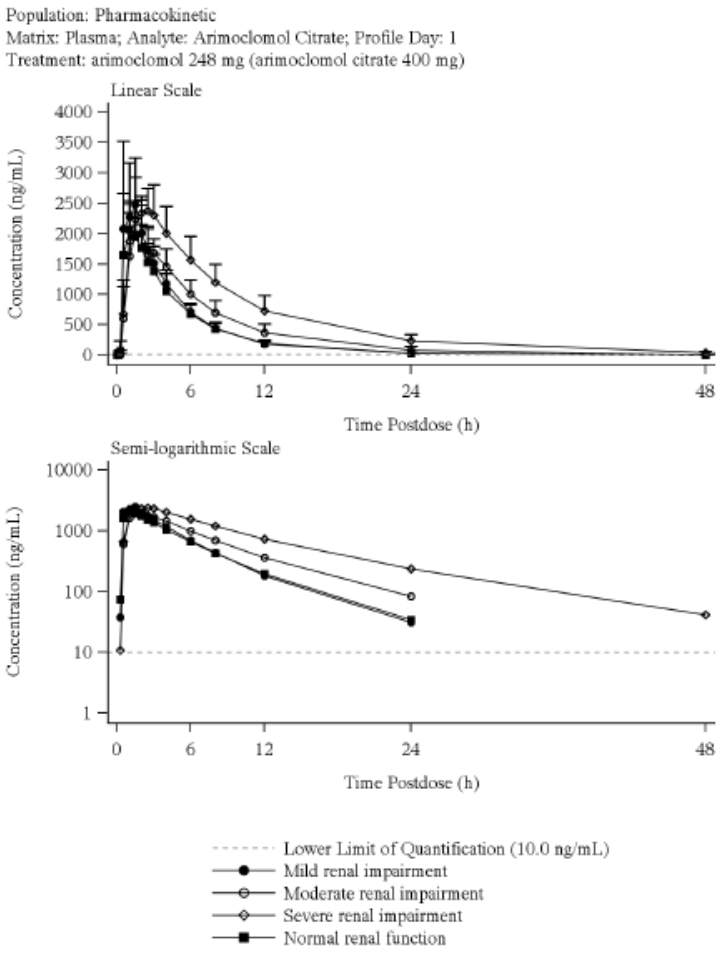
Following administration of a single dose of 248 mg arimoclomol to subjects with mild, moderate, or severe renal impairment or subjects with normal renal function, arimoclomol citrate was rapidly absorbed, with median **tmax** values of 0.75, 1.50, 2.01, and 1.25 hours, respectively.

Values of geometric mean **t1/2** were similar for subjects with mild renal impairment or normal renal function, with values of 3.76 and 4.31 hours, respectively.

Systemic exposure, when assessed by geometric mean arimoclomol citrate **AUC0-inf**, appeared to increase with the severity of renal impairment. There were statistically significant increases of 40% and 142% in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function because the 90% CIs (1.1611 to 1.6903 and 2.0281 to 2.8850, respectively) did not span unity. Subjects with mild renal impairment had a 9% increase in exposure to arimoclomol citrate compared to subjects with normal renal function when assessed by AUC0-inf, but this increase was not statistically significant because the 90% CI (0.9213 to 1.3011) spanned unity.

For **Cmax**, there was a statistically significant 34% increase in subjects with mild renal impairment compared to subjects with normal renal function because the 90% CI (1.0887 to 1.6579) did not contain unity. Subjects with moderate or severe renal impairment had values of Cmax that were similar to subjects with normal renal function, with 90% CIs (0.7899 to 1.2482 and 0.9180 to 1.4103, respectively) that spanned unity. Variability, as measured by geometric CV, was low for subjects with mild, moderate, or severe renal impairment and moderate for subjects with normal renal function, with values of 22.6%, 21.7%, 13.3%, and 26.4%, respectively.

Figure 2: Arithmetic Mean (+Standard Deviation) Arimoclomol Citrate Pharmacokinetic Concentration-time Profiles



Metabolite M2 and M105 Pharmacokinetic Parameters (Exploratory endpoints)

Table 10: Summary of the Metabolite M2 Pharmacokinetic Parameters

Matrix: Plasma; Analyte: M2; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Mild renal impairment (N = 8)	Moderate renal impairment (N = 8)	Severe renal impairment (N = 6)	Normal renal function (N = 8)
$AUC_{0\text{-}8h}$ (h*ng/mL)	3670 (15.8) [8]	4780 (45.7) [8]	8430 (27.8) [6]	3280 (25.8) [8]
$AUC_{0\text{-}t}$ (h*ng/mL)	7340 (21.9) [8]	15500 (61.9) [8]	61800 (43.5) [6]	6320 (28.0) [8]
$AUC_{0\text{-}inf}$ (h*ng/mL)	7410 (21.9) [8]	15700 (61.9) [8]	62400 (43.4) [6]	6420 (27.0) [8]
t_{max} (h)	4.00 (4.00-6.00) [8]	7.00 (6.00-8.00) [8]	10.01 (8.00-12.00) [6]	4.00 (4.00-4.00) [8]
C_{max} (ng/mL)	664 (15.4) [8]	981 (43.9) [8]	2140 (33.1) [6]	590 (28.9) [8]
$t_{1/2}$ (h)	7.42 (20.8) [8]	13.5 (47.5) [8]	30.2 (17.7) [6]	6.20 (20.5) [8]
MR_{AUC}	0.762 (23.9) [8]	1.31 (37.2) [8]	2.96 (27.8) [6]	0.717 (12.9) [8]
MR_{Cmax}	0.276 (25.3) [8]	0.563 (48.6) [8]	1.07 (26.2) [6]	0.335 (28.9) [8]
$MR_{AUC0\text{-}t}$	0.765 (24.1) [8]	1.34 (36.9) [8]	2.96 (27.7) [6]	0.719 (13.9) [8]

Table 11: Statistical Analysis of the Metabolite M2 Pharmacokinetic Parameters

Matrix: Plasma; Analyte: M2; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Renal Function Group	n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)
$AUC_{0\text{-}inf}$ (h*ng/mL)	Normal renal function (Reference)	8	5890	
	Mild renal impairment (Test)	8	7360	1.2496 (0.8879, 1.7588)
	Moderate renal impairment (Test)	8	16400	2.7856 (1.9206, 4.0402)
	Severe renal impairment (Test)	6	60100	10.2167 (7.2074, 14.4825)
C_{max} (ng/mL)	Normal renal function (Reference)	8	551	
	Mild renal impairment (Test)	8	655	1.1876 (0.8995, 1.5681)
	Moderate renal impairment (Test)	8	1050	1.8999 (1.4043, 2.5705)
	Severe renal impairment (Test)	6	2100	3.8096 (2.8687, 5.0591)

Table 12: Summary of the Metabolite M105 Pharmacokinetic Parameters

Matrix: Plasma; Analyte: M105; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Mild renal impairment (N = 8)	Moderate renal impairment (N = 8)	Severe renal impairment (N = 6)	Normal renal function (N = 8)
$AUC_{0\text{-}8h}$ (h*ng/mL)	209 (26.8) [8]	117 (67.4) [8]	114 (119.7) [6]	97.7 (93.7) [8]
$AUC_{0\text{-}t}$ (h*ng/mL)	3210 (43.7) [8]	5570 (39.4) [8]	18500 (46.2) [6]	2770 (36.4) [8]
$AUC_{0\text{-}inf}$ (h*ng/mL)	NC (NC) [0]	NC (NC) [0]	22400 (22.9) [5]	NC (NC) [0]
t_{max} (h)	24.00 (24.00-24.02) [8]	24.00 (24.00-24.03) [8]	47.94 (24.00-48.03) [6]	24.00 (23.98-24.00) [8]
C_{max} (ng/mL)	101 (44.5) [8]	156 (35.2) [8]	294 (41.5) [6]	93.0 (34.5) [8]
$t_{1/2}$ (h)	NC (NC) [0]	NC (NC) [0]	21.9 (19.8) [5]	NC (NC) [0]
MR_{AUC}	NC (NC) [0]	NC (NC) [0]	2.30 (33.7) [5]	NC (NC) [0]
MR_{Cmax}	0.0952 (59.9) [8]	0.204 (39.5) [8]	0.334 (29.9) [6]	0.120 (48.3) [8]
$MR_{AUC0\text{-}t}$	0.762 (46.2) [8]	1.09 (39.5) [8]	2.01 (41.1) [6]	0.715 (42.1) [8]

Table 13: Statistical Analysis of the Metabolite M105 Pharmacokinetic Parameters

Matrix: Plasma; Analyte: M105; Profile Day: 1
Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Parameter	Renal Function Group	n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)
$AUC_{0\text{-}t}$ (h*ng/mL)	Normal renal function (Reference)	8	2670	
	Mild renal impairment (Test)	8	3010	1.1282 (0.8268, 1.5393)
	Moderate renal impairment (Test)	8	6300	2.3610 (1.6838, 3.3106)
	Severe renal impairment (Test)	6	19300	7.2130 (5.2523, 9.9058)
C_{max} (ng/mL)	Normal renal function (Reference)	8	89.4	
	Mild renal impairment (Test)	8	95.2	1.0652 (0.7915, 1.4337)
	Moderate renal impairment (Test)	8	177	1.9836 (1.4358, 2.7404)
	Severe renal impairment (Test)	6	305	3.4072 (2.5159, 4.6144)

Safety (secondary objective):

All AEs were collected from the time that a subject signed the ICF until the subject attended the follow-up or withdrawal/discontinuation visit.

Two (25.0%) subjects in the mild renal impairment group, 1 (12.5%) subject in the moderate renal impairment group, 1 (16.7%) subject in the severe renal impairment group, and 2 (25.0%) subjects in the normal renal function group reported at least 1 TEAE. All 7 TEAEs were mild in severity; were considered by the investigator to be possibly related to the trial drug; and had resolved by the end of the trial without treatment. No serious TEAEs and no TEAEs leading to discontinuation were reported.f

Table 14: Summary of Treatment-emergent Adverse Events

Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

	Mild renal impairment (N = 8) nS (%) [nE]	Moderate renal impairment (N = 8) nS (%) [nE]	Severe renal impairment (N = 6) nS (%) [nE]	Normal renal function (N = 8) nS (%) [nE]
TEAEs				
Overall	2 (25.0%) [3]	1 (12.5%) [1]	1 (16.7%) [1]	2 (25.0%) [2]
Serious	---	---	---	---
Leading to Discontinuation	---	---	---	---
Leading to Death	---	---	---	---
Severity				
Mild	2 (25.0%) [3]	1 (12.5%) [1]	1 (16.7%) [1]	2 (25.0%) [2]
Moderate	---	---	---	---
Severe	---	---	---	---
Causality				
Not related	---	---	---	---
Possibly related	2 (25.0%) [3]	1 (12.5%) [1]	1 (16.7%) [1]	2 (25.0%) [2]
Probably related	---	---	---	---
Outcome				
Recovered/Resolved	2 (25.0%) [3]	1 (12.5%) [1]	1 (16.7%) [1]	2 (25.0%) [2]
Recovering	---	---	---	---
Not Recovered	---	---	---	---
Recovered with Sequalae	---	---	---	---
Fatal	---	---	---	---
Unknown	---	---	---	---

nE = number of adverse events; nS = number of subjects with an adverse event; N = number of subjects;
% = percentage of subjects with an adverse event (nS/N×100)
The nS (%) [nE] statistics presented.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred after administration of the IMP.
Where the severity of a TEAE was missing, a TEAE was counted under the maximum severity possible.
Where a subject experienced multiple TEAEs with the same preferred term for the same treatment, this was counted as 1 TEAE for that treatment under the maximum severity recorded.
Reference: Table 14.3.1-1
Program Location: /cvn/projects/prj/ecb/programs/000000188704/dev/tables/t_ae_itt.sas
Program Status: FINAL Program Run: 03SEP2021 Protocol Reference: OR-ARI-REN-01

A total of 6 subjects reported a total of 7 TEAEs in this trial.

• Headache was reported by 1 subject in each of the mild and moderate renal impairment groups and by 2 subjects in the normal renal function group.

• Diarrhoea and fatigue were both reported by 1 subject in the mild renal impairment group.

• Nausea was reported by 1 subject in the severe renal impairment group

Table 15: Frequency of Treatment-emergent Adverse Events (All Causalities)

Treatment: arimoclomol 248 mg (arimoclomol citrate 400 mg)

Preferred Term	Mild renal impairment (N = 8) nS (%)	Moderate renal impairment (N = 8) nS (%)	Severe renal impairment (N = 6) nS (%)	Normal renal function (N = 8) nS (%)
Overall	2 (25.0%)	1 (12.5%)	1 (16.7%)	2 (25.0%)
Headache	1 (12.5%)	1 (12.5%)	---	2 (25.0%)
Diarrhoea	1 (12.5%)	---	---	---
Nausea	---	---	1 (16.7%)	---
Fatigue	1 (12.5%)	---	---	---

There were no clinically significant findings in the clinical laboratory data, vital signs or body weight data, ECG data nor in the physical and neurological examination data.

Arimoclomol was well tolerated in the different groups of renal impaired patients with no severe AEs and few other AEs in general. All AEs resolved during the trial duration. None of the AEs were unexpected and all are covered adequately in the SmPC.

3.3.10. Discussion on clinical safety

For this full marketing application, the safety database consists of data from four clinical studies, of which only two are in the intended (orphan) indication. In CT-ORZY-NPC-002, a randomised, double-blind, placebo-controlled study consisting of a double blind (DB) and an open label (OL) extension phase, NPC patients aged 2-18 years old were treated with arimoclomol. Three studies were done in other indications, amyotrophic lateral sclerosis (AALS-001 - double-blind, placebo-controlled dose ranging safety and PK), AALS-001 OL (the open label extension of AALS-001), SOD1 ALS- randomised, placebo-controlled) and 1 study in sporadic inclusion bodies myositis (IBM10656 - randomised, double-blind, placebo controlled).

In the pivotal study CT-ORZY-NPC-002 50 patients were randomised 2:1 to treatment with arimoclomol (34 patients), or placebo (16 patients). From the 27 (79.4%) patients who completed the DB phase, 26 continued with arimoclomol in the OL phase. In addition, all 15 completers of the DB placebo arm (93.8%) switched to arimoclomol. The resulting safety database consists of 49 NPC patients who received 372 mg/day weight-adjusted arimoclomol. The daily dose depended on body weight groups and raged from 93 mg/day in the group 8-15 kg BW to 372 mg/day in the group >55 kg BW. In the other indications, 97 patients received doses ranging from 47 to 186 mg/day. In addition, 83 healthy volunteers received different doses ranging from 31-1116 mg/day in single dose and multiple dose studies.

The patients in study NPC-002 DB phase were exposed to the weight adjusted dose of 372 mg of arimoclomol for 306.9 days. In study NPC-002 OL so far, the mean exposure time was 688.8 days. The safety database is rather sparse. However, considered the severity of the disease and the rarity of this orphan disease (estimated 822 patients in EU), this can be accepted. Safety data in NPC patients are supported by complete study data investigating other indications, i.e. ALS and IBM. A weakness is the comparability between the NPC and ALS/IBM populations. The age difference (children vs adults), disease characteristics, dose difference (arimoclomol 372 mg weight-adjusted vs arimoclomol 47-372 mg); fixed doses, and the exposure difference; 12 months minimum in NPC versus 3-12 months in the other indications. Therefore, no direct extrapolation was attempted, and the safety data were purely used supportively to increase the possibility of finding uncommon safety events

The included NPC study population is considered representative for the intended target population and thus suitable to assess arimoclomol safety in the intended indication. Only paediatric patients were included in this study, of which only six patients (four patients treated with IMP and 2 with placebo in the DB phase) were under 4 years. In the D120 LoQ the applicant was invited to discuss how data from other age groups could be extrapolated to patients below the age of 4 years and to provide safety data separately for this age group. The applicant has provided data indicating no altered safety profile in patients 2-4 years of age. Results of a PopPK model further support this notion. However, since data are limited in those patients, the applicant added a warning in section 4.2 of the SmPC that data is limited in this population

Since the applicant intends to study the safety and efficacy in adult NPC patients post-marketing, the applicant was asked to comment on the co-morbidities that adult NPC patients display in comparison to

the young NPC population and discuss any expected adult-specific safety issues (for example, hepatic-/renal impairment). According to the applicant there are no known co-morbidities specific for adult patients with NPC, irrespective of whether their disease onset was during childhood or later. Regarding renal or hepatic function no big differences are to be expected, also having in mind the rather short life expectancy for patients with adult-onset NPC. Overall, based on the data provided, it can be expected that the safety profile in adult patients with NPC is similar to that of the paediatric population.

Concomitant medication is very common in NPC patients. Around 80% are on miglustat, currently approved in the EU for NPC. Stratification in the NPC-002 study was based on miglustat use. No AEs were reported significantly more in the patients in miglustat versus patients without. Drug-interaction studies have been performed and some interaction potential with OCT-2 substrates/MATE inhibitors in combination with arimoclomol was found. While no altered safety profile was found in the few patients that simultaneously used both medications, the applicant is invited to discuss this interaction in patients with renal and hepatic impairment. It should be noted that the renal impairment safety study (Trial OR-ARI-REN-01) is currently ongoing.

In study NPC-002, two patients died during the treatment period, one in the DB phase and one in the OL phase, both were on arimoclomol. The deaths were assessed as not related to the treatment. Based on the provided narratives this is acknowledged. In the other indications, 28 patients died, none were related to arimoclomol. The incidence rate of TEAEs was balanced between the treatment arms in the DB phase. The most frequently reported SOCs for NPC study were Infections and Infestations with nearly similar incidence in arimoclomol and placebo groups (67.6% vs 68.8%). Markedly higher incidence in armoclomol group was reported for Gastrointestinal Disorders (21/61.8% vs 6/37.5%), Nervous System Disorders (14/41.2% vs 3/18.8%) and Respiratory, Thoracic and Mediastinal Disorders (11/32.4% vs 3/18.8%), Investigations (8/23.5% vs 1/6.3%), Metabolism and nutritional disorders (6/17.6% vs 1/6.3%).

Patients on arimoclomol (14.7%) reported body weight decrease vs patients on placebo (0%). The applicant claims that the weight decrease was not clinically significant; however, given that normal growth and body weight dynamics are important safety criteria especially for younger patients, and in order to better evaluate clinical relevance of this finding, the applicant was asked to specify the age for patients with reported body weight decrease and discuss underlying reasons (e.g. other TEAs, such as gastrointestinal disorders, decreased appetite). The applicant responded that patients in whom an AE of *weight decreased* was reported in the DB phase of trial CT-ORZY-NPC-002, were between 10-18 years of age except for one 3-year-old patient. Data in younger patients in whom the BW dynamic is particularly important is missing. The applicant also discussed possible correlation between GI AEs and BW decrease from baseline in patients exposed to armoclomol. It has been acknowledged that although GI disorders may contribute to weight decrease, strong association between reported GI AEs and negative weight dynamic has not been demonstrated. The applicant proposes inclusion of a clarifying paragraph related to reported BW decrease in NPC patients treated with arimoclomol. This is endorsed.

In addition, it has been pointed that NPC patients have increased aspiration risk and the applicant was asked to clarify the risks associated with the accidental aspiration of the medicinal product and the possible effect on the bioavailability. The applicant provided an acceptable discussion on possible risks of accidental arimoclomol aspiration and preventive measures to minimise aspiration risk in NPC patients.

The applicant was asked to discuss whether growth related physiological weight gain has been taken into account assessing the long term arimoclomol effect on weight dynamics from baseline, particularly in younger patients. The applicant has clarified that data on height dynamic for children treated with arimoclomol were not systematically collected and therefore not available. Considering clinical

relevance of height dynamic in paediatric patients, it is recommended to foresee height monitoring in children exposed to arimoclomol as a part of postmarketing surveillance.

The applicant performed an additional analysis of all AEs in all clinical studies to identify adverse drug reactions for the representation in the SmPC. The applicant explained that rates of AEs were balanced between arimoclomol and placebo groups. However, there was a little overlap between the AEs observed in the other indication – restricting its usefulness. The identified AEs in the other indications are adequately described in the SmPC.

The applicant provided results of the recently completed TQT trial (OR-ARI-TQT-01 trial) in the D120 responses, showing that arimoclomol did not have a clinically relevant effect on heart rate or on cardiac conduction i.e., the PR and QRS intervals. Furthermore, the applicant performed a search using the SMQ Torsade de pointes/QT prolongation (broad scope) and SMQ Myocardial infarction across the clinical trials in order to evaluate any AEs related to effects on QT interval (including cardiac arrest and myocardial infarction). Based on this re-analysis there is no indication of a higher risk of events related to QT prolongation or myocardial infarction in patients treated with arimoclomol.

Rates of serious adverse events were generally low in the NPC studies and more frequent in the placebo group. In the other indications, equal rates between arimoclomol and placebo groups were observed. The events do partly correspond with the adverse events of special interest (SoC gastrointestinal). Further AEs of special interest were influenced by the findings in the non-clinical dataset, for which the applicant provided additional details in the D120 responses. Therefore, the AEs of special interest should include carcinogenicity, QT prolongation, SMQ Lens disorders, effects on SoC Immune system and SoC Infections and infestations, haematological parameters, and kidney injury.

- In the current safety dataset carcinogenicity, effects on fertility, or any effects on SoC Immune system or SoC Infections and infestations were not observed.
- Non-clinical data show QT prolongation in dogs and rats. No direct evidence regarding QT prolongation was identified in the safety database. The results from the QT prolongation safety study were provided in the D120 responses. The study demonstrated that arimoclomol has no negative effect on QT prolongation, therefore this is no longer a point of concern.
- Non-clinical data did show cataract formation in rats that was probably due to metabolite of arimoclomol accumulation in the lens. There were some eye-related AEs reported that are due to natural progression of the disease or due to ageing. Due to the limited safety pool and short time span of the study, during which it is considered unlikely that cataract formation or ocular toxicity occurs, the applicant was asked to discuss how ocular toxicity can be monitored and provide a discussion on how ocular toxicity could potentially affect the QoL for NPC patients. In the D180 responses, the applicant provided this discussion and stated that ocular toxicity will be added to the RMP as an important potential risk and will be monitored as an experimental endpoint in the PASS to further characterise this risk. Ocular toxicity will be monitored in the PASS by registrating all ocular events. Since it is unclear how (and if) ocular toxicity will manifest itself, keeping this as a broad term and gathering all ocular events from the small expected NPC population (~900 in the EU) would allow for the best possible characterisation of this risk.
- During clinical programme, in both NPC and ALS indications, patients on arimoclomol had creatinine values >1.5 from baseline and a total of 2 AEs of "proteinuria" were reported – giving rise to concerns regarding kidney injury. "Creatinine decreased" is adequately explained in the SmPC. The AE Proteinuria was considered unrelated to arimoclomol. Thus, these variations in the creatinine parameters are not a cause for concern.

Taken together, considering that, the target population falls in the paediatric age group, long-term exposure and corresponding effects carry a heavy weight. While admittedly few serious AEs were observed, the non-clinical findings coupled with clinical and laboratory observations, warrants an in-depth discussion by the applicant to alleviate the aforementioned concerns. Part of these concerns were recently addressed in the renal safety study or are part of the post marketing follow-up (carcinogenicity and ocular toxicity).

Post marketing follow-up (OR-REG-NPC-01) focuses on "urticaria with angioedema", "acute renal failure", and obtaining more treatment details. A paediatric sub-study is currently enrolling patients to study "Off-label use in patients below 2 years of age". Finally, rats studies are undergoing and will be finished in Q2/3 2021 to address the "carcinogenicity" concern.

During the clinical development programme, seven patients were discontinued in the DB phase, of which three due to TEAEs; blood creatinine increased, urticaria with angioedema, and another urticaria AE. These are adequately presented in section 4.8 of the SmPC. In the OL phase, further three patients were discontinued. One fatal event of lower respiratory tract infection, neurological decompensation + anaemia, and hypertonia + tremor. The fatal cases can be considered due to the disease progression and unrelated to arimoclomol use.

Arimoclomol is degraded by the liver and kidney. Some information has been provided concerning renal and hepatic impaired patients. No AEs were seen in mild or moderate hepatic impaired patients.

A recently finished single-dose trial (OR-ARI-REN-01), investigating the pharmacokinetic properties of arimoclomol in 30 subjects with mild (N=8), moderate (N=8) and severe (N=6) renal impairment and normal renal function (N=8) did not identify additional safety concerns that were not already known for arimoclomol. A total of 6 subjects reported a total of 7 TEAEs in this trial. All 7 TEAEs were mild in severity and had resolved by the end of the trial without treatment. No safety issues were noted during the trial. Systemic exposure, when assessed by mean arimoclomol citrate AUC0-inf, appeared to increase with the severity of renal impairment, with statistically significant 40% and 142% increases in subjects with moderate and severe renal impairment, respectively, and a not statistically significant 9% increase in subjects with mild renal impairment when compared to subjects with normal renal function. Furthermore, subjects with moderate or severe renal impairment had statistically significant 179% and 922% increases in exposure to metabolite M2 and statistically significant 136% and 621% increases in exposure to metabolite M105 when assessed by AUC0-t, compared to subjects with normal renal function. Additionally, subjects with moderate or severe renal impairment had statistically significant 90% and 281% increases to metabolite M2 and statistically significant 98% and 241% increases in exposure to metabolite M105 when assessed by Cmax, compared to subjects with normal renal function. There was no statistically significant increase in exposure to these metabolites for subjects with mild renal impairment compared to subjects with normal renal function when assessed by AUC0-t or Cmax.

Due to the observed increase in exposure to the two metabolites M2 and M105, the applicant suggests a dose reduction in severely renally impaired patients to half the recommended dose. This proposal is viewed critically as there are no efficacy data with half the recommended dose. Thus, the applicant is asked to provide a justification for the dose proposal made in the SmPC, otherwise a contraindication in patients with severe renal impairment is recommended. Furthermore, an adequate risk assessment on possible safety issues caused by an increase of systemic exposure to arimoclomol and its metabolites is currently missing and needs to be provided. This risk assessment should also include a discussion why no dose reduction for patients with moderate renal impairment is currently proposed, although a rather high exposure increase can be seen in this patient population too. (**OC**)

3.3.11. Conclusions on clinical safety

No MOs were raised.

The most common ADRs are non-serious in the SoC gastrointestinal disorders.

Currently the following uncertainties stem from the rather small study population and the lack of long-term data:

- No arimoclomol-related AEs regarding ocular toxicity were observed in the NPC studies. However, non-clinical studies have shown that arimoclomol accumulates in the eye and together with unspecific protein degradation, it can potentially cause ocular toxicity. This is currently included in the RMP.
- Recommended dose in severely renally impaired patients needs to be justified, otherwise a contraindication in patients with severe renal impairment is recommended.

3.4. Risk management plan

The applicant submitted RMP version 0.3 with data lock point 31 July 2020, date of final sign off 09 November 2021.

3.4.1. *Safety Specification*

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Acute renal failure Off-label use in patients below 2 years of age Ocular toxicity
Missing information	Carcinogenicity

3.4.1.1. Discussion of the safety specification

The proposed summary of safety concerns is accepted.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification no further issues need to be addressed.

3.4.2. Pharmacovigilance Plan

3.4.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

No specific adverse reaction follow-up questionnaires are planned, which is endorsed.

3.4.2.2. Summary of additional PhV activities

Summary of planned additional PhV activities from RMP

Table III-1 On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Not applicable				
Category 2 – Not applicable				
Category 3 - Required Additional Pharmacovigilance Activities				
Post-Authorisation Safety Study using data from the INPDR: a retrospective cohort study of patients exposed to arimoclomol or standard of care. (OR-REG-NPC-01) Planned	Primary objectives: To assess the incidence of acute renal failure with NPC treated routinely with arimoclomol Secondary objectives: To describe the use of arimoclomol as prescribed in routine practice in patients with Niemann-Pick Disease Type C in terms of: Treatment patterns (e.g., dose, duration) Patient characteristics at treatment initiation (e.g., age, symptoms severity) To describe the use of arimoclomol in children below two years of age and, if used, to assess its safety profile in this population To compare the incidence of acute renal failure between patients exposed to arimoclomol and not exposed to arimoclomol To compare the patient characteristics between patients with Niemann-Pick Disease Type C exposed to arimoclomol and not exposed to arimoclomol	Important potential risks: Acute renal failure Off-label use in patients below 2 years of age Ocular toxicity	Protocol submission	Three months after marketing authorisation in EU
			Annual progress reports	PSURs
			Final study report	6 years after market entry (expected Q1 2028)

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To assess the evolution of NPC symptoms during arimoclomol treatment as measured by the 5-domain NPCCSS. **Exploratory Objective** To explore any signal for ocular toxicity in patients treated routinely with arimoclomol			
Main study (CT-ORZY-NPC-002) Ongoing	**Primary Objective** To evaluate therapeutic response to arimoclomol versus placebo, both in addition to best available standard of care, at 12 months. **Secondary Objectives** To evaluate the therapeutic response to arimoclomol through clinical, biological and imaging assessments at 6 and 12 months; To evaluate the long-term therapeutic response (clinical and biological assessments) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months; To evaluate the safety of arimoclomol.	**Important potential risks** Acute renal failure Ocular toxicity	Final Clinical Trial Report	Q2 2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Paediatric substudy (CT-ORZY-NPC-002) Ongoing	Primary Objective To evaluate the safety and tolerability of arimoclomol in patients aged 6 to <24 months at study enrolment. Secondary Objectives To evaluate the therapeutic response to arimoclomol in patients aged 6 to <24 months at study enrolment through clinical, biological and imaging assessments. To assess the PK of arimoclomol and metabolites (if relevant), (dose/weight versus area under the curve in 0-8 hours at steady state [$AUC_{0-8,SS}$]) in patients aged 6 to <24 months at study enrolment.	Important potential risks Off-label use in patients below 2 years of age	Final Clinical Trial Report	Q4 2025
Rat carcinogenicity study (PQ64LW) Ongoing	The objective of the study is to assess the carcinogenic potential and toxicokinetics of arimoclomol.	Missing information Carcinogenicity	Final study report	Q3 2022

Cohort study using the International Nieman-Pick Disease registry (INPDR) (category 3)

The applicant proposes using the INPDR as data source for the conduct of a registry-based long-term safety PASS and submitted a synopsis of the study protocol. The choice of using the INPDR as data source for the conduct of a registry-based long-term safety PASS has been sufficiently justified by the applicant and is considered acceptable by the PRAC Rapporteur.

The INPDR is a web-based disease database established in 2013 and is currently populated with patient data from six different countries (the United Kingdom, Czech Republic, Spain, Italy, Ireland and Germany). As per April 2021, 93 NPC patients provide prospective data and their representativeness in relation to the sought indication for arimoclomol is considered acceptable. According to the applicant, recruitment projections are indicating that the database will increase with 400-600 patients from more countries within the coming 1-2 years. Also, in its recently published strategic business plan (2020-2022), the registry owners confirm this prospect of extending data collection and approaching maturity of the database. The INPDR collects two types of data: clinician-reported data (CRD) and patient-reported data (PRD). The CRD is provided by the patient's clinician and collects information on demographics, genetics, medical history/comorbidities, NPC symptoms, NPC disease outcomes and treatments, as well as on adverse drug reactions to NPC medications (start and end dates, relatedness,

action taken to suspected treatment), pregnancies and deaths. The PRAC Rapporteur considers latter safety endpoints especially relevant for the conduct of a safety PASS. Regarding data quality, the applicant explains that the INPDR is currently working on plans to further update the registry database (expected implementation in Q3 2021), and to improve data collection—promoting completeness and quality such as source data verification—in order to (re)submit a proposal for SAWP qualification. According to the applicant, the datapoints collected in the registry have also been revised to include the essential datapoints as recommended by the draft guideline (EMA draft guideline on registries Sep 2020). Such alignment of data elements in line with EMA recommendations is welcomed by the PRAC Rapporteur. Although the actual quality performance and level of recording of safety endpoints cannot yet be concluded, at this stage of the procedure, the efforts described to assure sufficient data collection, quality and representativeness with the INPDR are acknowledged by the PRAC Rapporteur.

From the synopsis of the protocol of above PASS study, the proposed descriptive analyses (primary objective) and comparative analyses (secondary objective) are considered acceptable, as well as the proposed comparator group (i.e., non-users: NPC patients not treated with arimoclomol), sample size (i.e., minimum of 200 NPC patients) and minimum follow-duration for each NPC patient (i.e., 2 months).

As requested in previous round, the applicant added off-label use in patients below 2 years of age as a safety concern to be studied with the latter observational safety PASS as well as Ocular toxicity (following CHMP comment).

A more detailed assessment of the study protocol will be performed in a separate procedure following submission of the full study protocol in case marketing authorisation is granted.

Open label study CT-ORZY-NPC-002 (ongoing)

As requested in previous round, the applicant included the open label study CT-ORZY-NPC-002 including 50 randomised patients aged > 2 years of age, where 41 patients continued into the open-label extension phase.

Paediatric sub-study (ongoing)

The inclusion of the paediatric sub-study of CT-ORZY-NPC-002 in the PhV plan to further characterise Off-label use in patients below 2 years of age (Important potential risk) is endorsed. The open label study CT-ORZY-NPC-002 includes an ongoing open label paediatric sub-study including patients aged 6 to <24 months at study enrolment, with the primary objective to evaluate the safety and tolerability.

OR-ARI-REN-01 trial (completed and removed from PhV plan)

In previous RMP versions (v0.1 and v0.2), the applicant included the interventional PK study (OR-ARI-REN-01 trial) investigating the PK properties of arimoclomol in subjects with mild, moderate and severe renal impairment and normal renal function in the PhV plan. OR-ARI-REN-01 trial investigated the PK properties of arimoclomol in subjects with mild, moderate and severe renal impairment. In current RMP version (v0.3) OR-ARI-REN-01 trial has been removed from the PhV plan; RMP v0.3 points out that OR-ARI-REN-01 trial was ongoing at the safety data cut-off, 31 July 2020, but the clinical trial report was completed before this submission of RMP v0.3. Considering the above, removal of latter trial from the PhV plan is considered acceptable. Reference is made to other parts of the dossier for assessment of the outcome of latter trial.

Rat carcinogenicity study (ongoing)
Inclusion of the ongoing non-clinical study in rats to assess the carcinogenic potential and toxicokinetics of arimoclomol is endorsed.

Note: RMP v0.3 also refers to finalisation of a phototoxicity study, but this study was not included as study in the PhV plan in previous RMP versions; thus, there is no need to update the PhV plan in this regard.

3.4.2.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product. Ocular event end-points are endorsed (see 3.3.10. Discussion on clinical safety).

The choice of using the INPDR as data source for the conduct of a registry-based long-term safety PASS is considered acceptable by the PRAC Rapporteur. According to milestones, the study protocol of the registry-based long-term safety PASS using the INPDR will be submitted within 3 months after the marketing authorisation approval.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

3.4.3.1. Routine Risk Minimisation Measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Acute renal failure	Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Enhanced ADR Collection from Participants in the INPDR Registry Prescribed Arimoclomol Additional pharmacovigilance activities: • OR-REG-NPC-01, final study report planned in Q1 2028 • CT-ORZY-NPC-002, final study report Q2 2023
Off-label use in patients below 2 years of age	Restricted medical prescription Routine risk communication: SmPC section 5.1 SmPC section 4.1 the indication is limited to patients above 2 years of age	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Enhanced ADR Collection from Participants in the INPDR Registry Prescribed Arimoclomol Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		• CT-ORZY-NPC 002- paediatric substudy, final study report planned in Q4 2025 • OR-REG-NPC-01, final study report planned in Q1 2028
Ocular toxicity	Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Enhanced ADR Collection from Participants in the INPDR Registry Prescribed Arimoclomol Additional pharmacovigilance activities: • OR-REG-NPC-01, final study report planned in Q1 2028 • CT-ORZY-NPC-002, final study report Q2 2023
Carcinogenicity	Restricted medical prescription	Additional pharmacovigilance activities: PQ64LW, final study report planned in Q3 2022

3.4.3.2. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.4. Summary of the risk management plan

The public summary of the RMP is considered acceptable for now, although further revisions may be required depending on comments made in other parts of the dossier and/or comments made in next rounds.

3.4.5. PRAC Outcome (September 2021)

The PRAC discussed during its September 2021 meeting the assessment by the PRAC Rapporteur of the applicant's responses to the D120 LoQ in relation to the RMP aspects (pharmacovigilance plan and risk minimisation measures) for the Miplyffa (arimoclomol citrate) RMP version 0.2 dated 15 July 2021. The Committee fully endorsed the assessment by the PRAC Rapporteur.

In particular, the PRAC supported the following way forward:

Pharmacovigilance plan:

- The proposed category 3 PASS using data from the International Niemann-Pick Disease (NPC) Registry (a retrospective cohort study of patients exposed to arimoclomol or standard of care, to assess the incidence of acute renal failure with NPC treated routinely with arimoclomol) is

considered acceptable. However, considering limited data of off-label use in patients below 2 years of age, the applicant should consider adding the important potential risk "off-label use in patients below 2 years of age" in the secondary objectives of the PASS.

- Ongoing open-label extended phase of study CT-ORZY-NPC-002 (to provide long-term safety information) including 50 randomised patients aged >2 years of age, where 42 patients completed the treatment phase and 41 of these patients continued into the open-label extension phase, is recommended to be included in the pharmacovigilance plan unless a sufficient justification for not including the study is provided. The applicant is therefore requested to discuss whether the open-label extended phase of study could further characterise any of the safety concerns such as "acute renal failure".

Risk minimisation measures:

- The proposed routine risk minimisation measures are considered sufficient to manage the safety concerns of the medicinal product at this stage, however the respective parts of the RMP should be also updated following the assessment of the safety specifications.

Besides, the PRAC discussed that despite existence of adult form of the disease (10% of cases), a low number of patients of childbearing potential is expected and that Miplyffa (arimoclomol) is contraindicated for use in pregnancy. The Committee suggested, for consideration of the CHMP Rapporteur's team, to reconsider the inclusion of "reduced fertility", "affected embryo-foetal development and survival" and "use during breastfeeding" as missing information in the safety concerns. The PRAC agreed that due to the contraindication for use in pregnancy and disease epidemiology, the impact of this potential safety issue on the benefit-risk balance would not be significant and further characterisation of this missing information via additional pharmacovigilance activities is not considered to be feasible. This comment is raised to the attention of the CHMP Rapporteur's team assessing the safety specification of the RMP for Miplyffa (arimoclomol citrate) and is left at their discretion.

All these specific aspects are included as individual questions in the RMP LoQ, which will require an RMP update.

3.4.6. Conclusion on the RMP

The PRAC Rapporteur considered that the risk management plan version 0.3 (data lock point 31 July 2020, date of final sign off 09 November 2021) is considered acceptable. Ocular event end-points to be evaluated may require further specification in the RMP, pending CHMP assessment of the safety specification. Reference is made to CHMP assessment. Hereupon, the variable section in the synopsis of study protocol of the registry-based long-term safety PASS using INPDR may be further updated accordingly **(OC).**

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Having considered the data submitted in the application, no pre-authorisation pharmacovigilance inspection is required.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. THE IBD will be the MAA approval date.

4. Non-Conformity with agreed Paediatric Investigation Plan

The Rapporteur is of the opinion that studies which are contained in the agreed Paediatric Investigation Plan, have been completed after 26 January 2007.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The target indication applied for by the applicant is the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older.

NPC is a rare, progressive, and fatal neurodegenerative disorder with an estimated incidence of ~1:100,000 live births (Geberhiwot et al. 2018). It is characterised by gradual loss of function that typically leads to death before adulthood. Overall, the mean life expectancy for patients with NPC is 13 years (Bianconi et al. 2019). It has substantial impact on all aspects of the life of the patients and their families.

NPC is an autosomal recessive disorder caused by mutations in the NPC1 (95% of cases) or NPC2 genes. Both genes encode lysosomal proteins that are essential in intracellular transport and metabolism of lipids. As a result of the dysfunction of either of these NPC proteins, lysosomal function is impaired causing an accumulation of lipids in the lysosomes, which in turn leads to cell stress and toxicity (Lloyd-Evans and Platt 2010; Platt et al. 2018). Over time, this leads to neurodegeneration as well as peripheral organ dysfunction.

The disease is characterised by a range of progressive and disabling symptoms including increasing difficulties with basic functions such as walking, motor coordination, swallowing, speaking, concentrating and remembering, leading to complete dependency on family and caregivers (Wraith and Imrie 2007). The progressive deterioration of brain function leads to a significant decrease in the quality of life of patients and their families (Benussi et al. 2018).

While manifesting most commonly during childhood and adolescence, NPC can present at any stage of life with highly diverse symptomatology and with variable speed and patterns of progression – from a neonatal, rapidly progressive fatal disorder to an adult-onset, slowly progressing, neurodegenerative disease. NPC can be categorised by age at onset 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 at onset of the neurologic symptoms. Earlier age at onset of neurological signs and symptoms is also predictive of rapid disease progression. Double functional null NPC1 genotype predicts an early infantile and severe NPC. No single symptom can predict the progression rate of the individual patient (Vanier 2010; Yanjanin et al. 2010).

Systemic signs of liver, spleen and lung involvement typically precede the disease-defining neurodegeneration. 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 ataplexy. The progression of the neurological symptoms is responsible for disability and premature death in most cases (Vanier 2010).

5.1.2. Available therapies and unmet medical need

At present there are no cure or disease-modifying therapies for NPC, and consequently there is a high unmet medical need for new treatment options (Geberhiwot et al. 2018). Given the progressive, debilitating, life limiting, and fatal nature of the NPC disease (i.e., high morbidity), there is an urgent need for treatments that delay disease progression.

Miglustat is authorised in the European Union (EU) for the treatment of progressive neurological manifestations in patients with NPC. Miglustat reversibly inhibits glucosylceramide synthase and thus works as a substrate reduction therapy.

The unmet medical need for novel treatment options remains high with patients continuing to have progressive neurodegeneration with fatal outcome. In a recent paper over an observation period of 50 years, 338 deaths caused by NPC with a mean age of 13 years were described and it was concluded that there was no significant change in survival over the last 20 years (Bianconi et al. 2019).

5.1.3. Main clinical studies

For efficacy evaluation, trial CT-ORZY-NPC-002 was considered the main source of evidence. The double-blind treatment phase of trial CT-ORZY-NPC-002 was a 12-month randomised, placebo-controlled, multi-national phase III trial in patients with NPC to assess the efficacy and safety of arimoclomol administered on top of the patient's routine clinical care (including miglustat where applicable).

The selected population consisted of male and female patients from 2 years to 18 years and 11 months of age, of any ethnicity, with a confirmed diagnosis of NPC, and at least one NPC-related neurological symptom at the time of screening. Eligible patients had either no prior miglustat treatment or were on stable dose of miglustat for at least 6 months prior to trial entry and had preserved ability to walk either independently or with assistance.

The patients were randomised 2:1 to receive arimoclomol (weight-based dosing) or placebo.

Randomisation was stratified by miglustat treatment yes/no. Patients <12 years of age had an arimoclomol single-dose PK evaluation performed before (and independent of) randomisation, to confirm an acceptable exposure level.

During the 12-month treatment phase, efficacy assessments for the primary endpoint (5-domain 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. For patients participating in both trials, End of Trial (Visit 2) in the observational trial CT-ORZY-NPC-001 was used as baseline (Visit 1) for the CT-ORZY-NPC-002 trial.

The open-label extension phase of trial CT-ORZY-NPC-002 consists of a treatment period with a duration of 48 months (or until arimoclomol has received US/EU marketing authorisation), where all patients receive arimoclomol. During the extension phase, efficacy is assessed every 6 months. The open-label phase is ongoing.

5.2. Favourable effects

- The main evidence of efficacy is based on a randomised, double-blind, placebo-controlled study including 50 patients.
- The primary objective of the study was to evaluate therapeutic response to arimoclomol versus placebo, both in addition to best available standard of care, at 12 months. This objective was met in the primary endpoint (change in the NPC disease severity based on the 5-domain NPC Clinical Severity Scale (NPCCSS) scores (ambulation, speech, swallow, fine motor skills and cognition) from baseline (Visit 1) to 12 months (Visit 6)) with borderline significance (p = 0.0456).
- Subgroup analysis revealed increased effect of arimoclomol in the primary endpoint in patients treated with miglustat as part of their routine clinical care, with a significant treatment effect of -2.06 in favour of arimoclomol (95% CI: -3.49;- 0.63; p = 0.0060) at 12 months compared to baseline.

5.3. Uncertainties and limitations about favourable effects

- Robustness of the effect estimates for the primary endpoint is questioned, and the results of the primary analysis may be too optimistic according to the sensitivity analysis addressing missing data handling
    - 3 out of 5 highly important individual symptom domains included in primary endpoint seem unaffected by arimoclomol treatment.
- Signals of slowed disease progression identified via primary endpoint cannot be mapped to endpoints such as CGI-I, used for anchoring during validation.
- Effect of arimoclomol in patients not receiving additional miglustat therapy remains uncertain due to extremely limited sample size (placebo: n=3, arimoclomol: n=8) and severe imbalances in patients' baseline characteristics (mean age 7 years in arimoclomol vs 15 years in placebo group; mean 5-domain NPCCSS in arimoclomol group vs placebo group was 13.3 vs 8.7, 3 patients with double functional null mutation indicating an aggressive disease course included in arimoclomol group only).
- It is unclear whether the enhanced effect of arimoclomol measured by 5-domain NPCCSS seen in miglustat co-treated patients is due to a potential synergistic effect or whether this effect is independent of miglustat and rather due to better balanced groups.
- Persistence of efficacy is questionable due to an increase in disease progression observed in the arimoclomol-arimoclomol group between 12 and 18 months of arimoclomol-treatment (mean change in 5-domain NPCCSS score: 1.4), finally showing that the level of worsening was similar to placebo-arimoclomol group at 18 months (mean change from baseline 1 to 18 months in arimoclomol group vs placebo group: 2.2 vs 2.1) and 24 months compared to time-point 0 (mean change from baseline 1 to 24 months in arimoclomol group vs placebo group: 2.4 vs 2.2).
- The effect of arimoclomol as shown in the placebo-arimoclomol group of the open label extended phase remains uncertain due to the slow disease progression in this group between 6 (mean 5-domain NPCCSS: 11) and 12 months (mean 5-domain NPCCSS: 11.5), despite not being treated with arimoclomol implicating that stability of the disease cannot be interpreted as an effect of arimoclomol treatment.

5.4. Unfavourable effects

Non-clinical

- Safety pharmacology studies demonstrated partial hERG inhibition by arimoclomol and its three main metabolites, M2, M5 and M105, with narrow (and partly still uncertain) safety margins to clinical exposure. Furthermore, QT prolongation was observed at supra-therapeutic arimoclomol exposure in dogs. For more detailed information on this unfavourable effect please consult the respective parts of section 3.2 of this overview.

Safety

- Non-clinical data did show ocular toxicity in rats and based on the biochemical properties of arimoclomol (accumulation in the eye) ocular toxicity could potentially occur during long-term treatment.

5.5. Uncertainties and limitations about unfavourable effects

Non-clinical:

Several uncertainties were identified with an unknown relevance for the benefit risk ratio of arimoclomol in patients. These uncertainties are either based on lacking investigations of relevant non-clinical endpoints, or on an uncertain relevance of non-clinical findings for arimoclomol patients:

Uncertainties to the benefit-risk ratio of arimoclomol pertaining to lacking non-clinical investigations:

- Incomplete carcinogenicity assessment (*cave*: the applicant will submit the missing 2-year carcinogenicity study PQ64LW in Wistar rats as a post-authorisation measure);
- Lacking antigenicity investigations and lacking investigations pertaining to the question whether arimoclomol denaturates healthy proteins;

Uncertainties to the benefit-risk ratio of arimoclomol pertaining to an uncertain relevance of non-clinical findings (generally observed at supra-therapeutic exposures) for patients:

- Toxicity to embryo-foetal development;
- Toxicity to fertility and the reproductive tract;
- Toxicity to the immune system;
- Gastrointestinal irritation and toxicity;
- Toxicity to the central nervous system;
- Ocular toxicity (lens alterations);
- Hepatic toxicity;
- Renal toxicity;
- Cardiac alteration observed in dogs apart from QT prolongation (p wave magnitude decreases and QRS prolongations).

For more detailed information on these uncertainties, please consult the respective parts of section 3.2 of this overview.

Clinical:

- The safety database is sparse in the claimed indication. A total of 34 NPC patients were exposed to arimoclomol in the DB phase, and 41 patients in the OL phase of study CT-ORZY-NPC-002.
- Lack of long-term safety data. Especially considering the target population falls in the paediatric age group, long-term exposure and corresponding effects carry a heavy weight.

5.6. Effects Table

Table Effects Table for Miplyffa (arimoclomol) in NPC disease (database lock: May 9th 2019, safety data cutoff July 31st 2020)

Effect	Short Description	Unit	Arimoclomol	Placebo	Arimoclomol vs Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
5 domain NPCCSS	Change in the NPC disease severity based on the 5-domain NPC Clinical Severity Scale (NPCCSS) scores (ambulation, speech, swallow, fine motor skills and cognition) from baseline (Visit 1) to 12 months (Visit 6)	Fold change from baseline	FAS: 0.7	FAS: 2.0	FAS: -1.40 MIG*: -2.06	FAS: 95% CI: -2.76, 0.03 p value = 0.0456 MIG*: 95% CI: -3.49; -0.63 p value = 0.0060 Uncertainties are: - highly important symptom domains seem unaffected - signals of slowed disease progression identifiable via the 5 domain NPCCSS scale cannot be mapped to CGI-I, used for anchoring during validation	CT-ORZY-NPC-002

Effect	Short Description	Unit	Arimoclomol	Placebo	Arimoclomol vs Placebo	Uncertainties/ Strength of evidence	References
Full scale NPCCSS without hearing in MIG*	Change in the NPC disease severity based on the full-scale NPC Clinical Severity Scale (NPCCSS) scores excluding hearing domain from baseline (Visit 1) to 12 months (Visit 6)	Fold change from baseline	0.39	3.28	-2.89	95% CI: -5.44;-0.33 p = 0.0282	CT-ORZY-NPC-002
NPC-cdb in MIG*	Change in the NPC disease severity based on NPC-cdb scores from baseline (Visit 1) to 12 months (Visit 6)	Fold change from baseline	-0.26	7.51	-7.77	95% CI: -13.35; -2.19 p = 0.0078	CT-ORZY-NPC-002
Unfavourable Effects							
Ocular toxicity	Eye abnormalities		None	None		The non-clinical findings regarding ocular toxicity and Arimoclomol accumulation in the eye could result in ocular toxicity – this is not observed during the clinical development programme but it is questionable whether this is due to study limitations (few patients and short observation period) or whether this remains a theoretical concern.	Non-clinical

* MIG: Subgroup analysis using only patients co-treated with miglustat

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

A borderline treatment effect favouring arimoclomol over placebo was observed in the primary endpoint (change in 5-domain NPCCSS) at 12 months, reaching statistical significance in the FAS (p =0.0456), which is more pronounced in the patient subgroup co-treated with miglustat (p = 0.0060). However, robustness of the effect estimates for the primary endpoint is questioned, and the results of the primary analysis may be too optimistic according to the sensitivity analysis addressing missing data handling.

Even though the benefit of a combinatorial treatment regimen using arimoclomol and miglustat together could also be demonstrated by 5-domain NPCCSS and NPC-specific secondary endpoints, conclusions on the effect of arimoclomol used as monotherapy cannot be drawn based on the presented data provided from the DB phase. First of all, number of patients in the non-miglustat group is exteremely limited, and secondly, there were several imbalances in baseline data making it difficult to compare non-miglustat placebo with non-miglustat arimoclomol cohort, and hence, a conclusion on effectiveness of arimoclomol in patients not treated with miglustat cannot be given. Most importantly, however, it is currently still unclear whether the effect seen is based on miglustat co-treatment and a potential synergistic effect, or whether the effect seen is independent of co-treatment and rather based on better balanced groups in the miglustat co-treated groups.

Furthermore, it remains difficult to differentiate whether the stabilisation of the score values was due to an arimoclomol effect or due to the natural disease course, and the extent of bias in the comparison with external controls is unclear. The persistence of the treatment benefit beyond 12 months should leverage the randomisation in study 002 and allow considering the RCT part of study 002 together with its open-label extension part as a "randomised start design".

Regarding safety, only few serious adverse drug events were observed in the clinical studies. However, due to the limited patient population and short-term exposure, the current provided clinical data may not sufficiently address uncertainties found in (pre)clinical trials, e.g. ocular toxicity. The impact of potential ocular toxicity on the quality of life of NPC patients is currently not clear, but this will be characterised in the PASS study. The QT prolongation safety study alleviated concerns about arimoclomol negatively affecting QT prolongation. The recently completed renal safety study did not identify new safety concerns in renally impaired patients. However, an increase of systemic exposure to arimoclomol and its metabolites has been observed in patients with moderate and severe renal impairment. For the latter group of patients, the applicant proposes halving of the dose, but considering the lack of data with this dose, this needs to be properly justified.

Input from an *ad hoc* expert group (AHEG) will be asked to provide an expert opinion on the favourable and unfavourable effects of arimoclomol in Niemann-Pick disease type C in patients. The AHEG will also provide opinion on maintenance of effect of arimoclomol (LoOI).

5.7.2. Balance of benefits and risks

Even though limitations of the study due to the rarity and heterogenous nature of the disease are acknowledged, robustness of the effect estimates for the primary endpoint is questioned, and the results of the primary analysis may be too optimistic according to the sensitivity analysis addressing missing data handling. The effect seen is enhanced and statistically significant in the subgroup including the majority of study participants, the group co-treated with miglustat. This is also the group in which baseline 5-domain NPCCSS values are similar and comparable in placebo and arimoclomol-treated group, hence the result of this analysis, even though it was an exploratory subgroup analysis, should not be ignored. Support from NPC specific secondary endpoints not closely related to the primary endpoint is weak, but again, support in the miglustat co-treated group could be shown. However, although the miglustat co-treated subgroup shows statistically and clinically relevant results, due to the methodological issues associated with exploratory subgroup analyses and lack of pharmacological rational, this is not considered sufficient and convincing evidence of benefit for arimoclomol treatment. Additive or synergistic effects of arimoclomol and miglustat could not be convincingly demonstrated. Clinical effects in patients only treated with arimoclomol cannot be assessed due to very limited number of patients included in the trial and extremely different baseline 5 domain NPCCSS scores.

Persistence of the potential effect of arimoclomol in the OLE study is still uncertain as it is currently impossible to differentiate whether stabilisation of disease is due to the natural course itself or due to the effect of arimoclomol treatment.

Although major safety concerns could not be detected in the clinical programme, the (pre)-clinical safety uncertainty of ocular toxicity remains. It is of concern that potential ocular AEs could simply not be observed in the studies presented due to limited sample size and short treatment period. This concern will be monitored in the post-marketing PASS study. The renal safety study has been completed and did not identify new safety concerns. However, an increase of systemic exposure to arimoclomol and its metabolites in patients with moderate and severe renal impairment has been noted. For the latter group of patients, the applicant proposes halving of the dose, but considering the lack of data this needs to be further justified. Nevertheless, arimoclomol's clinical safety profile is currently deemed favourable.

Overall, the data presented do not confirm efficacy, neither in short-term treatment nor in long-term maintenance, and therefore the benefit/risk for arimoclomol in the claimed indication is currently not considered positive.

5.7.3. Additional considerations on the benefit-risk balance

N/A

5.8. Conclusions

The overall B/R of Miplyffa is currently negative.