Statistical Analysis Plan

CT-ORZY-NPC-002

Arimoclomol prospective double-blind, randomised, placebo-controlled study in patients diagnosed with Niemann - Pick disease type C

Study Period: 12 months (double-blind study phase)

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Version: Final Version 5

The undersigned have reviewed and revised this SAP and find it to be consistent with the study requirements:

[redacted] Chief Medical Officer, Orphazyme A/S — Sep 10, 2018
Date

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GLOSSARY OF ABBREVIATIONS

%CV	Coefficient of Variation
9HPT	9 Hole Peg Test
AE	Adverse Event
ALT	Alanine Transaminase
AM	Arithmetic Mean
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AP	Alkaline Phosphatase
AST	Aspartate Transaminase (also SGOT)
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Plasma Concentration Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body Weight
CAS	Completers Analysis Set
CDISC	Clinical Data Interchange Standards Consortium
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	Confidence Interval
Cmax	Maximum observed plasma concentration
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria Adverse Event
CV	Coefficient of Variation

DBL	Database Lock
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DOB	Date of Birth
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
E	Number of Events
ECG	Electrocardiogram
ECRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl-Transferase
GM	Geometric Mean
HDL	High-Density Lipoprotein
ICH	International Committee on Harmonisation
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LLQ	Lower Limit of Quantification
LS Mean	Least Squares Mean
MA	Marketing Authorisation
MAR	Missing At Random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent to Treat
ml	Millilitre
n	Number of Patients

NCS	Not Clinically Significant
NPC	Niemann-Pick disease type C
NPC-CDB	NPC - Clinical Database
NPCCSS	NPC Clinical Severity Scale
PK	Pharmacokinetics
POP PK	Population Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
SARA	Scale for the Assessment and Rating of Ataxia
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
US	United States
WBC	White Blood Cell
WHO	World Health Organisation
WHODD	World Health Organisation Drug Dictionary

1 INTRODUCTION

1.1 GENERAL

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Orphazyme Protocol CT-ORZY-NPC-002 and should be read in conjunction with the study protocol and electronic case report form (eCRF).

After each patient completes their 12 months visit they will be offered participation in an extension with open label arimoclomol. After the last patient has reached 12 months and data-cleaning is complete the study will be unblinded. This SAP describes the analysis to be conducted for the 12-month blinded study period only.

This version of the plan has been developed using the protocol Version 6.0 dated 13MAR2018 and annotated eCRF Version 2.0 dated 23MAR2017. Any further changes to the protocol or eCRF will be reviewed for potential impact on the SAP which will be amended if it is deemed necessary.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

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

2.2 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, 24, 30 and 36 months;
- To evaluate the safety of arimoclomol.

These objectives are taken from the study protocol. Analysis on long term data (i.e. data beyond 12 months) will be presented in a separate SAP.

3 STUDY DESIGN

3.1 OVERVIEW

This study is a prospective, randomised, double-blind, placebo controlled therapeutic study in male and female patients with confirmed diagnosis of Niemann-Pick disease type C (NPC) 1 or NPC 2 on miglustat therapy. Patients must have either completed the end of study (EOS) visit of the CT-ORZY-NPC-001 study or they must meet the eligibility criteria of the CT-ORZY-NPC-002 study, including a requirement of stable treatment with miglustat for 6 months (if on miglustat therapy) prior to enrolment into the CT-ORZY-NPC-002 study.

The purpose of this study is to assess the efficacy and safety of arimoclomol (compared to placebo) when it is administered as an add-on therapy to the patient's current prescribed best standard of care, where each patient's standard of care may, or may not, include miglustat.

Approximately 15-20 sites in 6-9 countries in Europe will participate in the study with patients being stratified according to whether they are on miglustat therapy (strata A) or not on miglustat therapy (strata B). Up to 52 NPC patients will be randomised, to have at least 40 evaluable patients (at least 30 of these should be paediatric patients less than 18 years of age). Patients will be randomised to receive placebo or arimoclomol at a ratio of 1:2.

Dosing is based on the patient's body weight. Patients less than 12 years of age will undergo an arimoclomol single-dose pharmacokinetic (PK) evaluation before randomisation in order to confirm the selected dose.

The study consists of a controlled blinded phase study period where patients will be administered the study drug (arimoclomol or placebo), orally three times a day (t.i.d.) as an add-on therapy to the patient's current prescribed best standard of care, for the duration of 12 months. The primary analysis for this study will be conducted for the 12-month blinded study period only.

Following this period, all patients will be offered to continue into the extension stage of the study where they will receive arimoclomol in addition to the best standard of care and attend site visits at 18, 24, 30 and 36 months after patient randomisation. The extension phase will run for 24 months or until arimoclomol has received European Union (EU)/United States (US) marketing authorisation (MA) or until the analysis of data from the controlled, 12-month blinded phase study period does not support the efficacy and/or safety of arimoclomol. If the EU/US MA is not obtained within this period, the duration of the study will be extended accordingly. Patients will be enrolled in the extension phase only if the investigator deems that the patient is deriving clinical benefits from participating in the trial.

Patients below 2 years of age will be enrolled in the study at a later time point. The current protocol will be amended to include this subpopulation when juvenile toxicology data is available to support dosing in patients below the age of 2 years and sufficient PK information is available from 30% of the patients less than 12 years of age.

Patients below 2 years of age will be treated with open label arimoclomol and will be analysed and reported in a separate document to the main analyses of the 12-month placebo-controlled study.

A Data Safety Monitoring Board (DSMB) will review all safety data.

During the study, if a patient's disease progression is too severe and/or too fast, an early escape clause will allow the investigator to apply the escape route which implies that the patient can be treated with arimoclomol during the blinded phase of the study. See protocol section 10.5.2 for more information on the early escape clause and how it is implemented.

3.2 INCLUSION AND EXCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfil all inclusion criteria and not violate any exclusion criteria (for the protocol under which they are entered) during screening prior to randomisation. Details of the inclusion and exclusion criteria are presented in the protocol.

3.3 STUDY TREATMENT

Arimoclomol or placebo will be dispensed in capsule form of 25 mg, 50 mg or 100 mg and will be administered orally t.i.d. If required, the study drug can 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 a dissolved or dispersed state, the study drug can also be administered via a gastric tube.

During the blinded phase study period, if the study drug administration coincides with the administration of other concomitant medication then the study drug should be administered first.

Dosing is based on the patient's body weight (BW):

Patient Body Weight	Arimoclomol Dose
8-15 kg BW	50 mg t.i.d. (150 mg/day)
>15-22 kg BW	75 mg t.i.d. (225 mg/day)
>22-38 kg BW	100 mg t.i.d. (300 mg/day)
>38-55 kg BW	150 mg t.i.d. (450 mg/day)
>55 kg BW	200 mg t.i.d. (600 mg/day)

The patient's weight will be measured at each visit to ensure that the correct dose is given and can be adjusted as required.

If a patient is receiving 150mg/day of study drug and they require a dose reduction, then a dose of 75 mg/day (25 mg t.i.d.) should be administered.

To confirm the dose for patients less than 12 years of age, a single arimoclomol dose PK evaluation will be performed, by an independent assessor, to verify the area under the curve from 0 to 8 hours (AUC_{0-8}). If a dose reduction is required, then another single arimoclomol dose PK evaluation will be performed to confirm the corresponding dose. This procedure will be repeated until the correct dose level is found.

In the event that an unexpected PK profile is obtained in a patient less than 12 years of age, which is clinically significant and could potentially impact the safety of the patient (e.g. risk of accumulation), then the independent assessor can recommend additional PK sampling to be performed.

3.4 STUDY TIMEPOINTS

The study consists of a 12 month, blinded, placebo-controlled phase and an extension phase in which all patients are treated with arimoclomol. The primary analysis for this study will be conducted for the 12-month blinded study period.

The extension phase is planned to run for 24 months or until arimoclomol has received EU/ US MA or until the analysis of data from the blinded phase study period does not support the efficacy and/or safety of arimoclomol. If the EU/US MA is not obtained within the 24-month period, then the duration of the study will be extended accordingly.

Visits and visit windows will be as follows:

Phase	Visit	Timepoint	Window
Screening			
PK*	1		
Randomisation			
Blinded Phase	2	7-14 days after start of continuous treatment	
	3	3 months after randomisation	± 4 weeks
	4	6 months after randomisation	± 4 weeks
	5	9 months after randomisation	± 4 weeks
	6	12 months after randomisation	± 4 weeks
Extension Phase	7	18 months after randomisation	± 4 weeks
	8	24 months after randomisation	± 8 weeks
	9	30 months after randomisation	± 8 weeks
	10	36 months after randomisation	± 8 weeks

*Only patients less than 12 years of age will receive a single oral dose of arimoclomol, which will be followed by PK sampling.

If more than one visit occurs within a window, the nearest to the scheduled time will be presented within the summaries but all data will be included in patient listings.

See Section 16.1 for the Study Flow Charts.

3.5 SAMPLE SIZE CONSIDERATIONS

No formal statistical calculation has been used to determine sample size.

A similar study (ASIS-001) with 15 patients reported a mean rate of progression as 3.6 points per year and the standard deviation (SD) was 2.2. Assuming this SD and a simple two sample t-test, it is required to randomise 30 patients to arimoclomol and 15 patients to placebo in order to have 80% power to detect a difference between arimoclomol and placebo of approximately 2 units on the NPC Clinical Severity Scale (NPCCSS) at the 5% significance level. Use of covariates and a repeated measurements model is expected to improve the power and allow a smaller difference to be detected.

Thus, up to 52 NPC patients will be randomised, in order to have at least 40 evaluable patients (at least 30 of these should be paediatric patients less than 18 years of age). A dropout rate of approximately 23% is estimated, and patients who drop out will not be replaced.

During the study, recruitment may be increased based on an assessment on the number of evaluable patients in the study to date.

For a submission to the FDA, it has been requested that Clinical Global Impression - Improvement (CGI-I) be included as a co-primary endpoint, but a requirement that the significance level for this endpoint being $P<0.05$ may not be necessary (given that the study was not designed or powered for this endpoint). Below are example power calculations for 5% and 10% significance levels for CGI-I, based on 50 randomised patients.

The blinded data pooled across the two treatment arms, shows approximately 70% of patients in the trial have remained stable or improved; approximately 30% have declined. If the relative risk of remaining stable (or improving) is 2.0 (arimoclomol vs. placebo), this would mean that approximately 28 (84%) and 7 (42%) patients in the two groups, respectively, would be classed as responders.

Similarly, if the relative risk of remaining stable (or improving) is 1.5 (arimoclomol vs. placebo), this would mean that approximately 26 (80%) and 9 (53%) patients in the two groups, respectively, would be classed as responders.

The Table below shows the power that the study has to detect relative risks in the range of 1.5 to 2.0 at the 2-sided 5% and 10% significance levels. The calculations are based on a chi-squared test with continuity correction.

	Power at Significance level:	
Relative risk	5%	10%
1.5	47%	59%
1.6	55%	67%
1.7	67%	77%
1.8	74%	83%
1.9	78%	87%
2.0	85%	91%

Based on this information, obtaining a significance level of 5% or 10% may be possible.

Statistical significance at this level, in addition to establishing statistical significance on the 5 domain NPCCSS at the 5% level, would provide sufficient evidence of a positive and meaningful effect of arimoclomol over placebo.

3.6 RANDOMISATION

Patients who are eligible for the study will be stratified into either strata A if they are on miglustat therapy or strata B if they are not on miglustat therapy.

At randomisation, the eCRF will assign a randomisation number to each patient. The treatment assigned to each patient is determined according to a computer-generated randomisation list. Patients will be randomised using an allocation ratio of 1:2, where for every 3 patients, 1 patient will receive placebo and 2 patients will receive arimoclomol. A total of 52 patients are expected to be randomised.

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINT

The primary endpoint for statistical comparison between treatment groups will be the change in the NPC disease severity based on the 5 domain NPCCSS scores (ambulation, speech, swallow, fine motor skills and cognition), from baseline (Visit 1) to 12 months (Visit 6).

Baseline is defined as the latest assessment prior to randomisation.

4.2 CLINICAL STATUS ENDPOINTS

The following list details all clinical status endpoints to be analysed. Treatment comparisons will only be made at 6 and 12 months, since all patients will be taking arimoclomol after 12 months.

- Responder analysis of Patient's CGI-I score remains stable or shows improvement at 12 months (note that for the FDA submission, this endpoint is considered a co-primary endpoint)
- Responder analysis of Patient's 5 domain NPCCSS score remains stable or improves at 12 months compared to baseline

  ["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 their 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). The MCID will be determined and documented prior to unblinding the study.
- Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 6 and 12 months.
- Change in full scale NPCCSS apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 12 months;
- Change in 5 domain NPCCSS score at 6 months;
- Changes in each individual domain of the NPCCSS at 6 and 12 months;
- Change in the NPC Clinical Database (NPC-CDB) score (modified "Stampfer Score") at 6 and 12 months;
- Change in Quality of Life (EQ 5D Y) at 6 and 12 months;
- Change in the Scale for Assessment and Rating of Ataxia (SARA) score at 6 and 12 months;
- Change in the Nine-Hole Peg Test (9HPT) at 6 and 12 months;
- Clinical Global Impression Scale - Severity (CGI-S) at 6 and 12 months;
- Clinical Global Impression Scale - Improvement (CGI-I) at 6 and 12 months.

4.3 EXPLORATORY ENDPOINTS

The following exploratory endpoints will be compared between treatment groups:

- NPC disease progression rate based on the NPCCSS scores from baseline in the CT-ORZY-NPC-002 study to 6 and 12 months;
- The number of patients leaving the blinded phase of the study before 12 months as a result of early escape;
- The number of patients who either withdraw from the study before 12 months, or who need to jump to escape therapy;

- Change in use of NPC medication/standard of care (including miglustat therapy) at 12 months.

4.4 IMAGING ENDPOINTS

Changes in the size of the liver and spleen (assessed by ultrasound) will be analysed at 6 and 12 months.

4.5 BIOMARKER ENDPOINTS

The following biomarkers will be explorative to confirm and support clinical observations and characterise the individual patient clinical status at baseline, 6 months and 12 months.

- NPC1 active protein;
- NPC1 protein function (cholesteryl esterification);
- Oxysterol (cholestane-3β, 5α, 6β-triol);
- Un-esterified cholesterol;
- HSP70;
- Glycosphingolipids;
- Sphingoid bases

4.6 OTHER ENDPOINTS

Patient acceptability/palatability of the study drug will be analysed during the blinded phase study period.

4.7 PK

Sampling for Population PK (POP PK) will be performed in all patients at 3, 6, 9 and 12 months, in order to perform an exploratory exposure-response analysis.

For safety reasons, for patients less than 12 years of age, a single arimoclomol dose PK evaluation will be performed. Additional assessments can be performed in the event of unexpected PK profiles.

4.8 SAFETY ENDPOINTS

Safety will be evaluated by the following endpoints:

- Adverse events (disease related and/or treatment/procedure related)
- Laboratory parameters (haematology, clinical chemistry)
- Vital signs

5 DEFINITIONS

Study Drug. Study drug to be taken is either arimoclomol or placebo.

Baseline. Baseline is defined by patient and by variable as the last non-missing value before randomisation.

Study Day. Study day is the number of days since start of treatment where the date of first dose is counted as Day 1.

Protocol Deviation: a deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment. This refers to any change, divergence, or departure from the study design or procedures defined in the protocol. Deviations recorded by the Project Manager or CRA, or detected by data management or by statistical programming checks will be identified and discussed at the Data Review Meeting (DRM) before database lock (DBL).

Major Protocol Deviation: These are defined as protocol deviations that are liable to bias the evaluation of the main efficacy endpoint. The following deviations will be considered as major (non-exhaustive list):

- Non-compliance with any inclusion or exclusion criteria which affects efficacy;
- Non-compliance with the study treatment. Compliance (%) = (Total number of administered doses during the period / total number of scheduled doses during the period) * 100. A patient is considered compliant if compliance >=80%;
- Intake of prohibited medication (any Investigational Medicinal Product (IMP) or any product not approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (FDA).

6 ANALYSIS SETS

Membership of the analysis sets will be reviewed and agreed at a DRM before database lock.

6.1 FULL ANALYSIS SET

The Full Analysis Set (FAS) (also called modified Intent to Treat (mITT)) is defined as those patients who were randomised and who have received at least 1 dose of randomised treatment medication (excl. single dose of arimoclomol (patients less than 12 years of age) for the assessment of PK prior to initiation of their randomised treatment).

The CT-ORZY-NPC-002 Protocol Version 6.0 dated 13-Mar-2018 defines 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 has been updated to the above.

The FAS will be used for all efficacy analyses. If any patients receive the wrong treatment in error, they will be analysed as randomised for efficacy analyses. Patients who use the escape route will be censored at the point where they start rescue medication (open label arimoclomol).

6.2 PER PROTOCOL SET

The Per Protocol (PP) set is defined as those patients who have taken at least 80% of their study drug medication up to the 6-month assessment (Visit 4) and have an assessment at 6 months or beyond. This will exclude all patients with less than 6 months of follow up data. The 80% of medication criterion will 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, will also be excluded from the PP set.

The PP set will be used for selected efficacy analyses (see Section 11.3). Patients who receive the wrong treatment in error will be excluded from these efficacy analyses.

If there are no exclusions from the FAS, the tables using the PP set will not be produced.

6.3 COMPLETERS ANALYSIS SET

The Completers Analysis Set (CAS), is defined as those patients who have taken at least 80% of their study drug medication up to the 12-month assessment (Visit 6) and have, as a minimum, assessments at baseline and at 12 months (± 8 weeks). Also, patients without a confirmed diagnosis of NPC, if any, will be excluded from the set.

The CAS will be used for selected efficacy analyses. Patients who receive the wrong treatment in error will be excluded from these efficacy analyses.

If there are no exclusions from the FAS, the tables using the CAS will not be produced.

6.4 SAFETY SET

The safety set is defined as all patients who have received at least one dose of study drug.

The safety set will be used for all safety analyses.

Since all patients less than 12 years of age will receive a dose of arimoclomol for PK assessment, even if they are randomised to placebo, the safety analysis will be presented by treatment period. See Section 11.4.1 for more details.

Patients who use the escape route will be censored at the point where they start rescue medication (open label arimoclomol). All AEs occurring after a dose of rescue medication is taken will be presented in a separate listing.

7 SAFETY MONITORING

No safety monitoring reports will be provided by Orion statistics department.

8 INTERIM ANALYSES

No interim analysis is planned during the 12 month double blind part of the study.

9 DATA

9.1 eCRF DATA

CRF data will be provided by Orion data management to the statistics department as SAS data sets in Orion standard format which will be used for programming the outputs to be included in the CSR. Populated data sets will be available when programming starts. These may contain dummy data if real data is not yet available.

9.2 EXTERNAL DATA

Laboratory samples will be analysed centrally by the following laboratories and sent to Orion:

- Covance, Switzerland - haematology and clinical chemistry
- Covance, UK - blood sample biomarkers (NPC1 protein function/cholesteryl esterification, oxysterol, unesterified cholesterol, HSP70), skin punch biopsy and PK sample data
- Covance, US - haematology and clinical chemistry
- Orphazyme, Denmark – glycosphingolipids, NPC1 protein and sphingoid bases

Data received as external transfers will be converted to SAS datasets by Orion data management and provided to the statistics department with the other CRF data.

No other external data will be received by Orion.

9.3 RANDOMISATION LIST

The randomisation list will be uploaded to a SAS dataset following database lock.

9.4 PROGRAMMING AND DATA REVIEW

Programming of analysis datasets, tables, figures and listings will be ongoing during the data management of the study. Outputs for the DSMB will be reviewed, but no formal quality control (QC) will take place. Blind outputs may be reviewed by Orphazyme before DBL.

When the final data is considered clean, key listings (to be agreed) will be run and distributed to the study team for review. A blinded DRM will be held to discuss the outcome of this review, the imputations for the primary endpoint and the protocol deviations. Once all data issues have been resolved and the analysis populations approved, the database will be locked. The final run of outputs and QC will then take place.

10 STATISTICAL METHODS

10.1 GENERAL PRINCIPLES

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

Data will be summarised by treatment group. A total column showing all patients will be included for baseline and safety summaries. Where appropriate, data will also be summarised by visit with summaries for each visit attended as scheduled and an additional summary for final (last scheduled visit or early withdrawal). The format of the summaries is defined in the shells at the end of this document.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard error [SE], SD, median, minimum and maximum) will be presented when relevant. Least Squares mean (LS mean), SE and 95% confidence interval (CI) will be presented in the statistical analysis outputs as appropriate. For PK summaries, arithmetic mean (AM), geometric mean (GM) and coefficient of variation (%CV) will be used to summarise the data. The minimum and maximum statistics will be presented in summary tables to the same number of significant figures as the original data. The mean/AM, median, LS mean, GM, CI, SD and SE will be presented to one more significant digit than the original data.

For numeric data which includes non-numeric values (e.g. PK data reported as BLQ or lab results reported as < 10 or >100) the following principles will be applied when summarising the data:

- BLQ will be replaced with a value that is ½ of the lower limit of quantification (LLQ)
- Results reported as < x will be treated in the same way as BLQ with LLQ=x
- In all other cases with non-numeric values AM, GM, SD, CI and %CV will not be calculated
- Whenever meaningful, minimum, median and maximum will be presented based on the reported data (e.g. minimum = <10, median = 20, maximum = >100)

In summary tables of categorical variables, the number of non-missing observations by category will be presented with percentages. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the column. All percentages will be presented to one decimal place.

Classifications of medical history, concomitant medication and adverse events will be sorted by descending overall frequency within the summary tables.

If any laboratory assessments are repeated at the same visit, the result from the repeat assessment will be used in summaries. Both values will be listed.

Data collected on the eCRF will be presented within data listings. The data listings will be sorted by treatment group, country, centre number, patient number and visit/week/day. Treatment group will be as allocated (randomised). If any patients receive the wrong treatment this will be flagged in all listings. Visits outside the visit windows will be identified within the listings.

The date format for all output presentations will be 'ddMMMyyyy'.

All statistical analysis will be performed using SAS 9.3 or higher.

All hypothesis testing will be carried out at the 5% (2-sided) significance level, although for the co-primary endpoint requested by FDA of CGI-I, some flexibility in the interpretation of the p-value may be acceptable (see Section 3.5 for justification).

P-values will be rounded to four decimal places. P-values less than 0.0001 will be reported as <0.0001 in tables.

If any of the assumptions underlying the formal statistical methods proposed are seen to be violated during the analysis of the final data, alternative statistical methods will be used and any changes documented in the statistical methods section of the clinical study report (CSR), including the rationale for use.

10.2 Missing Data

There will be no imputation of missing data for the primary endpoint and the continuous key secondary endpoint analyses in this study. If a baseline value is missing, no change from baseline will be calculated. For the responder key secondary endpoints, a patient who discontinues before 12 months will be considered a non-responder.

Sensitivity analyses will be performed using a multiple imputation approach, a tipping analysis approach and a non-parametric analysis. See Section 11.3.4 for more details.

10.3 Pooling of Sites

Sites will be pooled for all analyses. There will be no adjustment for site effect or treatment by site interaction.

11 STATISTICAL OUTPUT

General principles for layout of the statistical output are described in Section 10.1, including specification of the table columns, and these are illustrated for each unique table in the table shells in Section 15. For clarity and brevity in this document the phrase "by treatment group" is understood for all summaries and is not included within the text of this section.

The study analysis will be performed following database lock upon the last patient completing 12 months or upon his/her early discontinuation, whichever occurs first.

11.1 PATIENT DISPOSITION

The number (%) of patients who complete or withdraw from the study and the main reason for withdrawal will be summarised for all randomised patients (Table 14.1.1).

The patient disposition table (Table 14.1.2) will summarise the following data for all randomised patients:

- The number (%) of patients in the FAS
- The number (%) of patients in the PP set
- The number (%) of patients in the CAS
- The number (%) of patients in the safety set

A data listing presenting the eligibility for the analysis sets for each patient will be presented.

Protocol deviations will be reviewed and classed as major or minor during the blind DRM. A listing of all patients with protocol deviations will be presented.

11.2 PATIENT CHARACTERISTICS AT BASELINE

Baseline is defined by patient and by variable as the last non-missing value before randomisation.

11.2.1 Demographic and Baseline Characteristics

Age at enrolment (Visit 1) will be presented as age at last birthday as an integer.

Age, gender, race, ethnicity, height, weight and BMI will be summarised using the FAS and safety set (Table 14.1.3.1 and Table 14.1.3.2).

Age at first neurological signs is collected on the NPC disease history page and will be presented within the same table.

Overview of the enrolment of patients participating in CT-ORZY-NPC-001 whom continued into CT-ORZY-NPC002 will be presented in tabular form (Table 14.1.3.3).

11.2.2 Medical History and Current Medical Conditions

All conditions will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) defined in the Data Management Plan (DMP). Past medical/surgical

history (conditions that stopped prior to or at the screening visit) and current medical conditions (classified as 'ongoing') will be summarised by system organ class (SOC) and preferred term (PT). The number (%) of patients reporting each condition will be presented using the FAS and safety set (Table 14.1.4.1.1 to Table 14.1.4.2.2).

11.2.3 Characteristics of the Disease

NPC disease history including date of initial symptom and description, date of first neurological symptom, date of diagnosis confirmed by filipin staining (if applicable), confirmation of diagnosis by elevated cholestane triol/oxysterols, date of diagnosis confirmed by DNA sequence analysis, NPC diagnosis and mutation, history of neurological manifestations and current treatment with miglustat is collected as part of the screening process.

The following will be summarised (Table 14.1.5.1) using descriptive statistics:

- Time since first NPC symptom(s) (years) - calculated using date of initial symptom and date of Visit 1
- Time since first neurological symptom (years) - calculated using date of first neurological symptom and date of Visit 1
- Time since DNA disease confirmation (years) - calculated using date of diagnosis confirmed by DNA sequence analysis and date of Visit 1
- Time since NPC diagnosis (years) - calculated using date of NPC diagnosis on NPC-CDB Patient History Questionnaire and date of Visit 1
- Patient History NPC-CDB Score - taken from NPC-CDB Patient History questionnaire

NPC diagnosis (NPC1/ NPC2/ NPC1 and NPC2), history of neurological symptoms (yes/no) and current treatment with miglustat (yes/no) will also be summarised, in the same table, by number and proportion of patients. Filipin staining results (if available), descriptions of initial symptoms and descriptions of NPC mutations will be presented in the data listings.

For each individual symptom in the NPC-CDB history questionnaire the number and percentage of patients experiencing that symptom and mean age of onset of the symptom will be summarised (Table 14.1.5.2).

For each patient, all symptoms will be listed, along with age of onset for each.

11.2.4 Procedures/Non-Drug Therapies

All procedures/non-drug therapies recorded on the CRF will be listed only.

11.3 EFFICACY ANALYSES

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

11.3.1 Primary Efficacy Analysis

A general linear mixed model for repeated measurements will 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 is derived as the sum of scores from the ambulation, speech, swallow, fine motor skills and cognition domains.

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 (Table 14.2.1.1).

The analysis model is:

$$Y_{ijk} = \beta_0 \cdot y_{ij0} + T_i + M_l + V_k + TV_{ik} + s_{ij} + e_{ijk}$$

where

Y_{ijk} is the 5 domain NPCCSS endpoint for the j^{th} patient of treatment group i at visit k

y_{ij0} is the baseline value for the j^{th} patient of treatment group i

β_0 is the unknown fixed slope for the baseline covariate

T_i is the unknown fixed effect of treatment i

M_l is the unknown fixed effect of miglustat level l

V_k is the unknown fixed effect of visit k

TV_{ik} is the unknown fixed interaction effect of treatment i and visit k

s_{ij} is the effect associated with the j^{th} patient of treatment i

e_{ijk} is the error (residual) associated with the j^{th} patient of treatment i at visit k

s_{ij} and e_{ijk} are assumed to be independent from each other and follow a multivariate normal distribution. The covariance matrix for e is chosen to be the unstructured variance-covariance matrix, it assumes pair-wise correlations are not constrained by the data.

The estimated treatment effect is taken from the TV_{ik} interaction term at Visit 6 (i.e. 12 months).

Missing data will not be imputed for the primary endpoint analysis. If a baseline value is missing, no change from baseline will be calculated.

The primary endpoint analysis will be repeated for the PP set and the CAS (Table 14.2.1.2 and Table 14.2.1.3).

11.3.2 Secondary Efficacy Analyses

11.3.2.1 Key Secondary Endpoints

Responder analyses will be performed using the following definitions:

1. Patient's CGI-I score remains stable or shows improvement at 12 months (note that for the FDA submission, this endpoint is considered a co-primary endpoint)
2. Patient's 5 domain NPCCSS score remains stable or improves at 12 months compared to baseline

These will be analysed using two-tailed chi-squared tests on the FAS and will be repeated for the PP set and the CAS (Table 14.2.2.1.1 to Table 14.2.2.1.3 for CGI-I and Table 14.2.2.2.1 to Table 14.2.2.2.3 for 5 domain NPCCSS). If chi-squared conditions are not met, then a Fisher's exact test will be used. A patient who discontinues before 12 months will be considered a non-responder.

3. Time to worsening (months), as defined by reaching the MCID on patient's 5 domain NPCCSS.

Time to worsening (months) is 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) will be produced for each treatment group on the FAS and will be repeated for the PP set and the CAS (Figure 1.1 to Figure 1.3). The median time to worsening (months) for each treatment and the corresponding 2-sided 95% CI will be presented along with a two-sided log-rank test, stratified for use of miglustat, to compare time to worsening between the two treatments. This analysis will be produced on the FAS and will be repeated for the PP set and the CAS (Table 14.2.2.3.1 to Table 14.2.2.3.3).

4. The proportions of patients who have shown worsening by 6 months and by 12 months

Worsening is defined as patients that have reached the MCID on their 5 domain NPCCSS. This will be analysed using two-tailed chi-squared tests on the FAS and will be repeated for the PP set and the CAS (Table 14.2.2.4.1 to Table 14.2.2.4.3). If chi-squared conditions are not met, then a Fisher's exact test will be used. A patient who discontinues before 6 months (or 12 months, as appropriate) will be considered a patient who has worsened.

5. 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 will 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 will be repeated for the PP set and the CAS (Table 14.2.2.5.1 to Table 14.2.2.5.3). LS mean and mean difference in treatment will be presented along with 95% CIs and p-values. Full scale NPCCSS apart from hearing domains is derived as the sum of scores from all of the domains apart from Hearing and Auditory Brainstem Response.

11.3.2.2 NPCCSS Score

The 5 domain NPCCSS score and changes from baseline will be descriptively summarised at baseline and at 6 months on the FAS and repeated for the PP set and the CAS (Table 14.2.2.6.1.1 to Table 14.2.2.6.1.3).

The change in 5 domain NPCCSS score from baseline to 6 months will be analysed using an ANCOVA model including baseline 5 domain NPCCSS score, use of miglustat and randomised treatment as covariates on the FAS and repeated for the PP set and the CAS (Table 14.2.2.6.2.1 to Table 14.2.2.6.2.3). LS mean and mean difference in treatment will be presented along with 95% CIs and p-values.

Full scale NPCCSS apart from hearing domains and changes from baseline will be descriptively summarised at baseline and at 6 months on the FAS and repeated for the PP set and the CAS (Table 14.2.2.7.1.1 to Table 14.2.2.7.1.3).

The change in full scale NPCCSS apart from hearing domains from baseline to 6 months will be analysed using the same method outlined for the change in full scale NPCCSS apart from hearing domains at 12 months in Section 11.3.2.1 on the FAS and repeated for the PP set and the CAS (Table 14.2.2.7.2.1 to Table 14.2.2.7.2.3).

Scores and changes from baseline in each individual domain of the 5 domain NPCCSS (ambulation, speech, swallow, fine motor skills and cognition) and the other domains of the NPCCSS at 6 and 12 months will be summarised descriptively on the FAS and repeated for the PP set and the CAS (Table 14.2.2.8.1 to Table 14.2.2.8.3).

An increase in the NPCCSS score reflects a reduction in abilities.

11.3.2.3 NPC-CDB Score

Changes from baseline in the NPC-CDB (modified 'Stampfer score') at 6 and 12 months will be analysed using the same method outlined for the change in full scale NPCCSS apart from hearing domains at 12 months in Section 11.3.2.1 on the FAS (Table 14.2.2.9.1).

This table will be repeated for the PP set and the CAS (Table 14.2.2.9.2 and Table 14.2.2.9.3).

11.3.2.4 Quality of Life (EQ-5D-Y)

Quality of life (EQ-5D-Y) VAS scores at baseline, 6 and 12 months will be summarised descriptively (mean and median) on the FAS and repeated for the PP set and the CAS (Table 14.2.2.10.1.1 to Table 14.2.2.10.1.3).

The change in quality of life VAS score from baseline to 6 months and 12 months will be analysed using a Mann Whitney test and medians with 95% CIs will be presented for each visit on the FAS (Table 14.2.2.10.2.1).

This table will be repeated for the PP set and the CAS (Table 14.2.2.10.2.2 and Table 14.2.2.10.2.3).

The 5 individual items of the EQ-5D-Y will be summarised separately at baseline, 6 and 12 months to show the number (%) of patients in each category on the FAS and repeated for the PP set and the CAS (Table 14.2.2.10.3.1 to Table 14.2.2.10.3.3).

The 5 individual items of the EQ-5D-Y will be dichotomised at baseline, 6 and 12 months to show the number (%) of patients reporting any kind of problems (answer 2 or 3) vs no problems (answer 1) in each category on the FAS and repeated for the PP set and the CAS (Table 14.2.2.10.4.1 to Table 14.2.2.10.4.3). The change in number of patients experiencing no problem per item will be analysed for significance, but no statistical tests will be performed.

The change in the 5 individual items of the EQ-5D-Y per patient will be explored by using the pareto principle at 6 and 12 months to show the number (%) of patients who felt:

1) Better (better on at least one dimension and no worse in any other dimension),
2) Worse (worse in at least one dimension, and no better in any other dimension),

3) Mixed (better on one dimension, but worse on another) or
4) Exactly the same.

The number (%) of patients in the above four categories will be presented at 6 months compared to baseline and repeated at 12 months compared to baseline. A two-sided chi-square test will be performed to test for a treatment difference in the 'Better' category at 6 months and for 12 months on the FAS and repeated for the PP set and the CAS (Table 14.2.2.10.5.1 to Table 14.2.2.10.5.3). This analysis will be repeated within the same table for the 'Worse' category at 6 months and repeated for 12 months.

11.3.2.5 SARA Score

Changes from baseline in the SARA score at 6 and 12 months will be analysed using the same method outlined for the change in full scale NPCCSS apart from hearing domains at 12 months in Section 11.3.2.1 on the FAS (Table 14.2.2.11.1).

This table will be repeated for the PP set and the CAS (Table 14.2.2.11.2 and Table 14.2.2.11.3).

SARA scores and changes from baseline at 6 and 12 months will be summarised descriptively on the FAS and repeated for the PP set and the CAS (Table 14.2.2.11.4 to Table 14.2.2.11.6).

11.3.2.6 9HPT Time

Changes from baseline in the 9HPT time (seconds) at 6 and 12 months will be analysed using the same method outlined for the change in full scale NPCCSS apart from hearing domains at 12 months in Section 11.3.2.1 on the FAS (Table 14.2.2.12.1).

This table will be repeated for the PP set and the CAS (Table 14.2.2.12.2 and Table 14.2.2.12.3).

9HPT time and changes from baseline at 6 and 12 months will be summarised descriptively on the FAS and repeated for the PP set and the CAS (Table 14.2.2.12.4 to Table 14.2.2.12.6).

11.3.2.7 CGI-S and CGI-I

CGI-S at 6 and 12 months will be summarised to show the number (%) of patients in each category on the FAS and repeated for the PP set and the CAS (Table 14.2.2.13.1 to Table 14.2.2.13.3).

CGI-I at 6 and 12 months will be summarised to show the number (%) of patients in each category on the FAS and repeated for the PP set and the CAS (Table 14.2.2.14.1 to Table 14.2.2.14.3).

The cumulative distribution of patients in each CGI-S category at 6 months (probability of attaining each category level, or worse) will be plotted by treatment on the FAS, and repeated at 12 months (Figure 2.1.1 and Figure 2.1.2).

The cumulative distribution of patients in each CGI-I category at 6 months (probability of attaining each category level, or worse) will be plotted by treatment on the FAS, and repeated at 12 months (Figure 2.2.1 and Figure 2.2.2).

11.3.3 Exploratory Efficacy Analyses

11.3.3.1 Rate of Disease Progression

The change in full scale NPCCSS apart from hearing domains (rate of disease progression) from baseline to 6 months will be analysed using an ANCOVA model, including use of miglustat and randomised treatment as covariates (Table 14.2.3.1.1). This analysis will be repeated for the PP set and the CAS (Table 14.2.3.1.2 and Table 14.2.3.1.3).

The analysis will be repeated for the rate of disease progression from baseline to 12 months within the same tables.

In addition, the same analyses but including annual progression rate in the CT-ORZY-NPC-001 study as a covariate will be conducted in the subset of patients who participated in the CT-ORZY-NPC-001 study.

11.3.3.2 Early Escape and Withdrawal

The number (%) of patients who leave the blinded phase of the study as a result of qualifying for early escape will be presented for the FAS and repeated for the PP set (Table 14.2.3.2.1 and Table 14.2.3.2.2).

The number (%) of patients who withdraw from the study before 12 months, including those who qualified for early escape will be presented in the same table.

11.3.3.3 Subgroup Analysis

Exploratory subgroup analyses will be performed on the primary and all key secondary endpoints. Point estimates of treatment differences with 95% CIs and proportions of treatment difference with 95% CIs will be presented for each subgroup where applicable (Table 14.2.3.3.1 to Table 14.2.3.3.3). For the third key secondary endpoint, time to worsening, only p-values from the log-rank test will be displayed. The subgroups to be analysed are:

- use or not of miglustat at randomisation
- genotype
- age at diagnosis of first neurological symptom. Categories are:
    - pre/peri-natal (onset at age < 3 months)
    - early-infantile (at age 3 months to < 2 years)
    - late-infantile (at age 2 to < 6 years)
    - juvenile (at age 6–15 years)
    - 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) will be analysed for patients with late infantile phenotype (age at the start of neurological symptoms: at age 2 to < 6 years)

Forest plots will be presented for each of the five endpoints (primary and key secondary, with the exception of the third endpoint) displaying the point estimates of treatment differences with 95% CIs or proportions of treatment difference with 95% CIs, by the subgroup categories mentioned above for the FAS (Figure 3.1.1 to Figure 3.1.5). These will be repeated for the PP and CAS (Figure 3.2.1 to Figure 3.3.5). There will be no forest plot presented for the third key secondary endpoint.

11.3.4 Sensitivity Analyses

The primary analysis will be repeated using 3 different imputation methods to estimate missing 5 domain NPCCSS scores at 12 months. Any patient with missing baseline NPCCSS data will have the median NPCCSS score for all patients imputed.

In the first method, a multiple imputation method will be used to account for missing data at 12 months, as follows:

1. The missing values are filled in *m* times to generate *m* complete data sets (using SAS PROC MI).

   This is done by fitting *m* linear regression models using patients with observed values for the endpoint and further covariates (these may be baseline covariates or measurements of the endpoint at earlier visits or others). Based on the fitted regression model, a new regression model is simulated from the Bayesian posterior predictive distribution of the regression parameters and is used to impute the missing values;
2. The *m* complete datasets are analysed by using standard statistical procedures (as relevant for the specific endpoint);
3. The results from the *m* analyses are combined for statistical inference (using SAS PROC MIANALYZE).

Multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. The method assumes that missing values are 'missing at random' (MAR), such that any systematic difference between the missing values and the observed values can be explained by differences in observed data. The method allows unbiased imputation for patients who progress quickly in their disease and subsequently qualify for early escape, since these patients will have a heightened disease severity score.

The primary endpoint, change from baseline to 12 months in the 5 domain NPCCSS score, will be analysed and presented in the same way as the primary analysis on the FAS and repeated for the PP set and CAS (Table 14.2.4.1.1 to Table 14.2.4.1.3).

The second method will be via a tipping point analysis. Patients in the placebo arm will have the median for the placebo arm imputed for their (missing) 5-domain NPCCSS score. Patients in the arimoclomol arm who have a missing month 12 5-domain NPCCSS score will have successively worse scores imputed. First, each will have a 1-point worsening (i.e. 1 point higher than baseline) imputed and the primary endpoint will be analysed and presented in the same way as the primary analysis on the FAS and repeated for the PP set and CAS; then each will have a 2-point worsening imputed and the primary analyses repeated. This procedure will continue until all patients have had the worst possible month 12 5-domain NPCCSS score imputed. (See Table 14.2.4.2.1 to Table 14.2.4.2.3)

In the third method, a non-parametric analysis will be used to account for missing data at 12 months as follows:

1. Patients who withdraw early will be assigned 'worst' scores for their 12 month NPCCSS (i.e. worse than all patients, regardless of their treatment assignment);
2. Transformation of baseline and post-baseline values for all patients (regardless of treatment groups) to standardized ranks (*i.e.,* ranks divided by the number of patients ranked plus 1, mean ranks in case of ties);
3. Determination of residuals from the linear regression of the NPCCSS standardized ranks on baseline NPCCSS standardized ranks;
4. Application of the two-sided Wilcoxon-Mann-Whitney test to these residuals. The standardized test statistic with a continuity correction of 0.5 is asymptotically standard normally distributed under the null hypothesis.

The median and 95% CI will be presented for the primary endpoint on the FAS and repeated for the PP set and CAS (Table 14.2.4.3.1 to Table 14.2.4.3.3).

The cumulative distribution of change from baseline in full scale NPCCSS score apart from hearing domains at 6 months (probability of attaining each score level, or worse) will be plotted, stratified by patients in each CGI-I category and by treatment on the FAS (Figure 4.1). This will be repeated at 12 months (Figure 4.2) and repeated for the change from baseline in 5 domain NPCCSS scores (Figure 5.1 and Figure 5.2).

The primary endpoint, change from baseline to 12 months in the 5 domain NPCCSS score, will be analysed in the same way as the primary analysis on the FAS, with the addition of age at entry to the study as a covariate (Table 14.2.4.4.1). The analysis will be repeated with the addition of age at first neurological symptoms as a covariate and presented in the same table. These analyses will be repeated for the PP and CAS (Table 14.2.4.4.2 and Table 14.2.4.4.3).

A further analysis of the primary endpoint (change from baseline to 12 months in the 5 domain NPCCSS score) will be carried out as a simple ANCOVA with the 12 month data as the response and baseline 5 domain NPCCSS score, use of miglustat and randomised treatment as covariates. This analysis will be performed on the CAS only, since no imputation for missing data at 12 months will be included (Table 14.2.4.5).

For the key secondary endpoint, Patient's CGI-I at 12 months (considered a co-primary endpoint for the FDA submission), a sensitivity analysis of the ranks of the 7 point scale will be analysed

using the Van Elteren test, stratified by use of miglustat. The analysis will be performed on the FAS and repeated for the PP set and CAS (Table 14.2.4.6.1 to Table 14.2.4.6.3).

11.3.5 Imaging Analyses

Ultrasounds will be performed at baseline, 6 and 12 months in order to document changes in the size of the liver and spleen. Results at baseline, 6 and 12 months and changes from baseline will be summarised on the FAS (Table 14.2.5).

Clinically relevant findings are also collected and will be presented as a listing.

11.3.6 Biomarker Analyses

Biological markers will 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 will be derived and summarised using descriptive statistics on the FAS (Table 14.2.6).

11.3.7 Study Drug Palatability and Acceptability

Patient palatability and acceptability of the study drug will be assessed 7-14 days after the start of dosing, and at 3, 6 and 12 months. A validated hedonic scale, that has been extensively used to assess palatability of flavoured medications in other studies, will be used by patients (or the patient's parent[s]/legal guardian[s]) to rate the palatability and acceptability of the study drug.

The number (%) of patients in each category for all the questions will be summarised at each visit on the FAS (Table 14.2.7) along with the method by which the patient ingests the study medication (swallow, disperse, GI tube).

11.3.8 PK Analyses

11.3.8.1 POP PK

In order to perform an exploratory exposure-response analysis, sampling for POP PK will be performed in all patients at 3, 6, 9 and 12 months as follows:

- Sampling at 3 and 9 months should be carried out 3 hours (± 1 hour) after dosing.
- Sampling at 6 and 12 months should be carried out 1.5 hours (± 30 mins), 3 hours (± 30 mins) and 4.5-6 hours after dosing.

Results from PK sampling will be summarised using descriptive statistics on the FAS, by dose group (Table 14.2.8).

POP PK will also be modelled and analysed in a separate report.

11.3.8.2 PK Profiling in Patients less than 12 years of age

For patients less than 12 years of age, PK sampling will be undertaken after a single arimoclomol dose at pre-dose (immediately prior to administration of the single dose of arimoclomol), 30 mins (±5 mins), 1 hour (±10 mins), 2 hours (±10 mins), 4 hours (±30 mins) and 8 hours (±30 mins). The patient will be required to fast and more details on the procedure can be found in the protocol.

The following parameters will be assessed:

- $AUC_{0\text{-}8h}$ – The area-under-the-curve, from time zero to 8 hours, calculated by the linear trapezoidal rule.
- C_{max} – The maximum whole blood concentration of arimoclomol measured during the 8-hour period.

Additional assessments can be performed in the event of unexpected PK profiles or if the patient requires a dose reduction.

Individual concentrations at each time point and PK parameters will be listed, along with age, dose and any dose reductions.

11.4 SAFETY ANALYSES

11.4.1 Adverse Events

All adverse events (AE) will be classified using the version of the MedDRA coding dictionary specified in the DMP.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset date on or after the date of first IMP intake. If an event start date is partial, then the start day, month, year or stop date will be used to determine if the event is treatment-emergent. If the classification of the AE cannot be determined from the data available, then the event will be considered treatment-emergent.

Since all patients less than 12 years of age will receive a dose of arimoclomol for PK assessment, even if they are subsequently randomised to placebo, TEAEs will be presented according to treatment period:

- Single dose treatment period: after single dose arimoclomol for PK assessment until 28 days after or until start of the continuous treatment period, whichever comes first;
- Continuous treatment period: after start of continuous treatment with blinded IMP until last dose of blinded IMP.

In addition to these, a Rescue Patients Safety Set is defined for patients who use the escape route in the study. Patients will be censored at the point where they start rescue medication (open label arimoclomol) and any AEs occurring after a dose of rescue medication is taken will be ascribed to arimoclomol treatment group.

All AEs will be listed.

TEAEs will be further classified as follows:

Severe TEAEs: Severity classified as ‘CTCAE Grade 3’, ‘CTCAE Grade 4’ or missing.

Serious TEAEs: Serious classified as ‘yes’ or missing.

Drug-related TEAEs: Relationship to study drug classified as ‘yes’ or missing and assessment specified as ‘definitely related’, ‘probably related’, ‘possibly related’ or missing.

Serious drug-related TEAEs: Both serious and adverse drug reaction, as specified above.

TEAEs related to study procedure: Relationship to study procedure classified as 'yes' or missing and assessment specified as 'definitely related', 'probably related', 'possibly related' or missing.

TEAEs related to study disease: Relationship to study disease, NPC, classified as 'yes' or missing

TEAEs leading to study drug discontinuation: Action taken classified as 'permanent discontinuation'.

TEAEs leading to death: outcome classified as 'fatal'.

TEAEs overall and in each of the above classifications will be summarised on the safety set for each of the treatment periods (Table 14.3.1.1 and Table 14.3.1.2). TEAEs that start in the single dose treatment period (or between the two treatment periods) and are ongoing in the continuous treatment period will be summarised separately (Table 14.3.1.3).

Summaries by SOC and preferred term will also be presented for TEAEs for each treatment period (Table 14.3.2.1.1 to Table 14.3.2.1.3). These tables will be repeated for Severe TEAEs, Serious TEAEs, Adverse Drug Reactions, Serious Adverse Drug Reactions, TEAEs related to study procedure, TEAEs related to study disease, TEAEs leading to study drug discontinuation and TEAEs leading to death by treatment period (Table 14.3.2.2.1 to Table 14.3.2.9.3).

A summary by SOC and preferred term will also be presented for TEAEs of Special Interest by treatment period (Table 14.3.2.10.1 to Table 14.3.2.10.3).

TEAE summary tables will show the number (%) of patients having at least one TEAE and the number of events in each treatment group and overall. Note: If a patient has multiple AEs with the same SOC/preferred term, these will be summarised once within the count for n (%) of patients, but each event will be counted within the number of reports E of each AE.

Any AEs occurring for patients in the Rescue Patients Safety Set will be presented in a separate listing.

All adverse events, AEs leading to withdrawal, and AEs in patients with abnormal laboratory tests recorded on the CRF will be listed by SOC and PT within the data listings.

11.4.2 Laboratory Data

Laboratory results will be carried out at all visits during the study with the exception of Visit 5 at 9 months after randomisation. The laboratory parameters are:

- **Haematology**: haemoglobin, red blood cell (RBC) count, platelet count, white blood cell (WBC) count, absolute neutrophil count (ANC), differential leukocyte count (bands, neutrophils, basophils, eosinophils, monocytes, and lymphocytes, expressed as a percentage of WBC)
- **Clinical chemistry**: sodium, potassium, chloride, magnesium, iron, calcium, phosphate, creatinine (serum), blood urea nitrogen (BUN), triglycerides, high-density lipoprotein (HDL)/ low-density lipoprotein (LDL), cholesterol, ALT, AST, total bilirubin, gamma-glutamyl-transferase (GGT), alkaline phosphatase (AP), lactate dehydrogenase (LDH) and albumin

Laboratory parameters (mean and change from baseline) will be summarised at each visit using descriptive statistics on the safety set (Table 14.3.3.1 to Table 14.3.3.2).

Shift tables will be produced for all laboratory parameters showing whether observed values are normal, low or high at baseline and each patient's final visit (Table 14.3.4.1 to Table 14.3.4.2).

Incidence of abnormal laboratory values and alert values by visit and overall will be summarised by laboratory parameter (Table 14.3.5.1 to Table 14.3.5.2).

Patient profiles for all laboratory parameters over time will be presented (Figure 6.1 and Figure 6.2) with one plot per laboratory parameter.

Plots of creatinine levels over time will be presented by patient. Plots of mean and median creatinine levels over time will be presented by treatment, with SD bars displayed with mean values. These will be repeated showing patients with and without concomitant miglustat use (Figure 7.1 to Figure 7.5).

If laboratory results are repeated at the same visit, the repeated result will be used in summaries (instead of the original one) provided the sample was taken within the visit window, otherwise the original result will be used.

All laboratory results will be listed.

Laboratory results at unscheduled visits will be included in the listings but will not be summarised.

11.4.3 Vital Signs

Blood pressure, pulse rate, respiratory rate and temperature (ear) are collected at all visits. Weight is measured at screening and then at every visit from 3 months after randomisation. Height is collected at screening only.

Mean and change from baseline in blood pressure, pulse rate, respiratory rate and temperature will be summarised for each visit they are collected at using descriptive statistics on the safety set (Table 14.3.6.1).

Weight will be summarised at each visit, along with changes from baseline, using descriptive statistics on the safety set (Table 14.3.6.2).

Plots of weight over time will be presented by patient and by treatment (with mean, SD bars and median) and will be repeated showing patients with and without concomitant miglustat use (Figure 8.1 to Figure 8.6).

Incidence of abnormal blood pressure, pulse rate, respiratory rate, temperature and weight by visit and overall will be summarised by parameter (Table 14.3.6.3).

Height and weight measurements collected at screening are used to derive BMI, and they will be summarised within the demography data only.

11.4.4 Physical Examination

A physical examination will be conducted at screening, 6 and 12 months and at every visit in the extension phase of the study. The status of the body system being assessed will be classified as normal, abnormal non-clinically significant (NCS) or abnormal clinically significant (CS).

Physical examination data will be listed only.

11.4.5 Electrocardiogram

A 12-lead ECG will be conducted at screening, 6 and 12 month visits. The result of the ECG assessment is classified as normal, abnormal NCS or abnormal CS.

The number and percentage of the patients with normal / abnormal NCS / abnormal CS ECG results will be summarised at each visit and overall (Table 14.3.7).

11.4.6 Pregnancy Test

For all female patients of childbearing potential, a urine pregnancy test will be performed at screening and at 12 months. Results of all pregnancy testing will be listed only.

11.5 Concomitant Medication

All medications taken by patients on entry to the study or during the study will be recorded in the CRF. Medications will be classified using the version of the World Health Organisation Drug Dictionary (WHODD) coding dictionary defined in the DMP. The Anatomical Therapeutic Chemical (ATC) Classification and WHO-DRUG PT will be used to list and summarise the data.

Prior medications are defined as all medications that started and stopped before date of first dose. Only medications where the stop date is prior to date of first dose will be considered prior. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to date of first dose then the medications will be considered as maintained medications.

Maintained medications are defined as all medications that started before date of first dose and their stop date is either ongoing at the end of the study or the stop date is on or after date of first dose. Partial start dates where the medication cannot definitely be considered as starting prior to date of first dose will lead to a categorisation of the medications as concomitant medications.

Concomitant medications are defined as all medications that started on or after date of first dose.

The number (%) of patients reporting the use of any prior medications and the number (%) of patients taking each drug by ATC classification (1st, 2nd and 4th levels) and PT will be summarised using the safety set (Table 14.3.8.1).

This table will be repeated for maintained and concomitant medications (Table 14.3.8.2 and Table 14.3.8.3).

NPC medications and anticonvulsant medications taken by patients throughout the study are recorded on the CRF and will be presented in data listings.

12 VALIDATION

All tables, figures and listings will be subject to independent quality control and visual review. Unique tables will be independently programmed. Findings will be documented in a quality control form and actions taken will also be documented.

The completed form will be reviewed and signed by both programmers and by the Head of Statistics.

13 LITERATURE CITATIONS/REFERENCES

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15 SHELLS FOR TABLES, FIGURES AND LISTINGS

The intended layouts for tables, figures and listings are presented. However, it may be appropriate for the Orion programmer to change the layouts, upon review of the data available, for completeness and clarity. The shells are presented separately and not as part of this document.

QCd output will be produced as Rich Text Format (.rtf) files for convenient inclusion in the CSR.

Subject to this, the following will apply:

- Layout will be landscape, fixed width, font size 8.
- Each output will have the heading:

  Orphazyme CT-ORZY-NPC-002 (left); date ddMMMyyyy (right)
- Table headings will define the analysis set used for the summary/analysis.
- All outputs will have a footer specifying the SAS program path and filename (left); page x/y (right)
- Tables will have a footer specifying the source listing
- Figures will have a footer specifying the source table or listing
- Additional footnotes will be included where appropriate for clarification.
- Treatment group and patient number and will be included in all listings.

16 APPENDICES

16.1 STUDY FLOWCHARTS

16.1.1 Blinded Phase Study Period: Patients Less Than 12 Years of Age

STUDY PHASE	SCREENING	PK	RANDOM-ISATION	BLINDED PHASE STUDY PERIOD				END OF BLINDED PHASE[x]	UNSCHEDULED VISIT[y]
	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	NA
PROCEDURES	NA	NA	NA	7-14 days after start of continuous treatment[w]-	3 months (±4 weeks) after randomisation	6 months (±4 weeks) after randomisation	9 months (±4 weeks) after randomisation	12 months (±4 weeks) after randomisation or within 4 weeks or withdrawal during blinded phase	NA
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics[a]	X								
NPC Diagnosis[b]	X								
NPC Disease History[c]	X								
Medical History (including Concomitant Disease)	X								
Physical Examination[d]	X#					X		X	
Weight	X#				X	X	X	X	
Vital Signs[e]	X#			X	X	X	X	X	
ECG[f]	X#					X		X	
Skin Punch Biopsy for Biomarkers Analysis	X#					X		X	

STUDY PHASE	SCREENING	PK	RANDOM-ISATION	BLINDED PHASE STUDY PERIOD				END OF BLINDED PHASE[x]	UNSCHEDULED VISIT[y]
	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	NA
PROCEDURES	NA	NA	NA	7-14 days after start of continuous treatment[w]-	3 months (±4 weeks) after randomisation	6 months (±4 weeks) after randomisation	9 months (±4 weeks) after randomisation	12 months (±4 weeks) after randomisation or within 4 weeks or withdrawal during blinded phase	NA
Haematology[g]	X#			X	X	X		X	X
Clinical Chemistry[h]	X#			X	X	X		X	X
Blood Sample for Biomarker Analysis[i]	X#					X		X	
Pregnancy test [j]	X							X	
Ultrasound (Liver and Spleen)[k]	X#					X		X	
NPCCSS[l]	X#				X	X	X	X	X
NPC-cdb score[m]	X					X		X	
SARA[n]	X					X		X	
9HPT[n]	X					X		X	
CGI-S & CGI-I[n]	X				X	X	X	X	
Quality of Life Scoring[n]	X#					X		X	
Concomitant Therapy[o]	X								
Adverse Events[p]	X								
Single Dose Arimoclomol Administration[q]		X							

STUDY PHASE	SCREENING	PK	RANDOM-ISATION	BLINDED PHASE STUDY PERIOD				END OF BLINDED PHASE[x]	UNSCHEDULED VISIT[y]
	Visit 1			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	NA
PROCEDURES	NA	NA	NA	7-14 days after start of continuous treatment[w]-	3 months (±4 weeks) after randomisation	6 months (±4 weeks) after randomisation	9 months (±4 weeks) after randomisation	12 months (±4 weeks) after randomisation or within 4 weeks or withdrawal during blinded phase	NA
PK sampling[r]		X							
Randomisation[s]			X						
IMP Dispensing[t]			X$		X	X	X	X*	(X)
IMP Return[t]					X	X	X	X	(X)
IMP Administration[t]			X						
POP PK Sampling[u]					X	X	X	X	
Patient Acceptability/ Palatability[u]				X	X	X		X	
Telephone Follow up[z]				X (every month [±7 days])					

#The following assessments do not need to be repeated at Visit 1 if these assessments have been performed within 7 days of Visit 1: Physical examination including body weight and height, vital signs, ECG, skin punch biopsy, haematology, biochemistry, blood sample for biomarker analysis, ultrasound (liver and spleen), NPC Disease Severity Scores and Quality of Life scoring.

a **Demographics** includes date of birth, sex and race.

b **NPC diagnosis** based on date of initial symptom(s) and symptom(s) description, date of clinical diagnosis and symptoms clinical status, date of confirmed genetic NPC diagnosis, DNA sequence analysis and, if applicable, date of fillipin staining result and cholestane triol/oxysterols.

c **NPC disease history** including date of first NPC symptom, history of neurological manifestations and past treatments.

d **Physical examinations** during the study will include the assessment of skin, head, neck, lymphatic, abdomen, respiratory, cardiovascular/peripheral vascular, central nervous and musculoskeletal systems as appropriate to determine general condition.

e **Vital signs** will include supine blood pressure, pulse rate, respiratory rate and temperature (ear).

f A **twelve-lead ECG** will be recorded over at least 10 seconds after the patient has rested supine on a bed for at least 5 minutes.

g **Haematology** samples to be sent to a central laboratory for analysis.

h **Clinical chemistry** samples to be sent to a central laboratory for analysis.

i **Biomarker** samples to be sent to a central laboratory for analysis.

j Urine **pregnancy test** for post-menarchal female patients.

k **Ultrasound** of the liver and spleen to document changes in the size of the liver and spleen and any clinical relevant findings.

l **NPC clinical severity scale (NPCCSS)**: Refer to NPCCSS template provided for use in the study.

m **NPC-cdb score**: Refer to the modified NPC-cdb template provided for use in the study.

n **SARA**: Refer to SARA template provided for use in the study.

9HPT: Refer to 9HPT template provided for use in the study.

CGI-S & CGI-I: Refer to CGI-S and CGI-I templates provided for use in the study.

Quality of Life (EQ-5D-Y [Proxy version]) scoring will be completed by the patient's parent(s)/legal guardian(s).

o **Concomitant therapy** includes all medication and medical procedures (including any unplanned diagnostic, therapeutic or surgical procedures) ongoing at or starting after the time of written consent.

p **Adverse events (AEs)**: ALL AEs which are ongoing at Visit 1 and those that occur during study conduct, i.e. from the time of written informed consent to the end of the extension phase of the study or patient withdrawal, will be recorded in the eCRF.

q **Single dose arimoclomol administration**: Patients less than 12 years of age will initially receive a single oral dose of arimoclomol, followed by PK sampling.

r **PK sampling**: For patients less than 12 years of age only. PK sampling will be performed following a single dose of arimoclomol: pre-dose (immediately prior to administration of the single dose of arimoclomol) and 30 min (±5 min), 1 hour (±10 min), 2 hours (±10 min), 4 hours (±30 min) and 8 hours (±30 min) following dosing.

The following information should be noted down:

1. The precise time of the blood sampling;
2. The precise time of the administration of food and liquid(s);
3. The type of liquid(s) administered;
4. The selected route for the single dose administration of arimoclomol including any type of liquid/soft foodstuff used for the administration (as applicable).

The patient will be required to fast as follows:

1. Food: At least 2 hours before the single dose administration and at least 2 hours following the single dose administration;
2. Liquids: Non-protein and non-fat liquids (e.g. juice) are allowed for up to 1 hour before the single dose administration and from 1 hour following the single dose administration;
3. Water can be administered at any time during the PK procedure.

In the event that the patient requires a dose reduction, the patient will be dispensed a further single dose of arimoclomol. Single dose PK evaluation will be performed following this single dose of arimoclomol in order to confirm the corresponding dose.

Should further dose adjustments be required based on the single dose PK evaluation, the above procedure will be repeated.

In the event that unexpected PK-profiles are obtained which are clinical significant and could potentially impact the safety of the patient (e.g. risk of accumulation), the independent assessor can recommend additional PK sampling to be performed. If agreed by the Sponsor's medical responsible person and the Principal Investigator, up to a maximum of 6 additional samples (corresponding to the full PK analysis set) can be taken at a subsequent visit prior to randomisation.

s **Randomisation** for patients less than 12 years of age will take place following confirmation of the selected dose scheme after PK analysis.

t **IMP dispensing and administration** for patients less than 12 years of age: Following confirmation of the corresponding dose, IMP (arimoclomol or placebo, as per the study randomisation) will be shipped to the patient, who will commence dosing upon receipt of it.

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

The patient's weight should be measured at each visit and the IMP dose should be adjusted as required and IMP dispensed as relevant.

During the blinded phase of the study, patients will be dispensed enough IMP for treatment as per the study flow chart.

[$]In the event that the IMP (arimoclomol or placebo, as per the study randomisation) is shipped to the patient, the investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone within 1 week following randomisation to confirm that the IMP has been received, the date that the patient has commenced IMP dosing and whether the patient has experienced any difficulties in taking the IMP.

[*]The patient will be dispensed with sufficient arimoclomol at Visit 6 to continue treatment (for patients who have not withdrawn from the study).

Early Escape Criteria Met: Should a patient meet the early escape clause and criteria, the patient should be offered and dispensed treatment with arimoclomol. The patient should continue with their current protocol schedule.

IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty blister packs]) to the site staff. The site staff should aim to follow up on the reasons for any missing IMP or other discrepancies noted after performing the relevant IMP accountability.

u **POP PK Sampling**: POP PK sampling will be performed for all patients as follows:

- Visits 3 & 5: 3 hours (±1 hour) following dosing.
- Visits 4 & 6: 1.5 hours (±30 min), 3 hours (±30 min) and 4.5-6 hours following dosing. Note: The last POP PK sample should be taken as late as possible but always before the subsequent dose of IMP.

v **Patient Acceptability/Palatability**: Refer to the hedonic scale template provided for use in the study.

w **Visit 2** will take place 7-14 days after the patient has commenced taking the IMP t.i.d. (continuous treatment). For patients less than 12 years of age, continuous treatment will commence following confirmation of the corresponding selected dose scheme.

x **End of Blinded Phase (Visit 6)**: The end of blinded phase visit (Visit 6) should take place 12 months (±4 weeks) after randomisation or within 4 weeks of patient withdrawal during the blinded phase. **Withdrawal from study**: Should a patient discontinue prematurely and choose to withdraw from the study during the blinded phase, all effort should be made to have the patient attend the site for the end of blinded phase visit (Visit 6) within 4 weeks of patient withdrawal. Should the patient (or the patient's parent[s]/legal guardian[s]) refuse to attend the end of blinded phase visit (Visit 6), the date and reason for study discontinuation (if known) will be recorded in the eCRF as a minimum.

z **Unscheduled visit**: The patient may attend the site for unscheduled visits should the patient experience an unacceptable rate of progression or should there be any safety concerns. IMP dispensing and return will take place in the event that a patient meets the early escape clause and criteria or a dose reduction has occurred.

- **Telephone follow up** to be performed every month (±7 days) for 6 months after the start of continuous treatment. Telephone follow-up includes follow-up on the status of the patient, whether the patient has experienced any new AEs or the worsening of any existing AEs, whether the patient has had a change in any prescribed medication, whether the patient has experienced any difficulties in taking the IMP and to confirm the weight of the patient.

16.1.2 Blinded Phase Study Period: Patients 12 Years of Age and Older

STUDY PHASE	SCREENING	RANDOM-ISATION	BLINDED PHASE STUDY PERIOD				END OF BLINDED PHASE[u]	UNSCHEDULED VISIT[v]
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	NA
PROCEDURES	NA	NA	7-14 days after start of continuous treatment[t]-	3 months (±4 weeks) after randomisation	6 months (±4 weeks) after randomisation	9 months (±4 weeks) after randomisation	12 months (±4 weeks) after randomisation or within 4 weeks of withdrawal during blinded phase	NA
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographics[a]	X							
NPC Diagnosis[b]	X							
NPC Disease History[c]	X							
Medical History (including Concomitant Disease)	X							
Physical Examination[d]	X#				X		X	
Weight	X#			X	X	X	X	
Vital Signs[e]	X#		X	X	X	X	X	
ECG[f]	X#				X		X	
Skin Punch Biopsy for Biomarkers Analysis	X#				X		X	
Haematology[g]	X#		X	X	X		X	X
Clinical Chemistry[h]	X#		X	X	X		X	X
Blood Sample for Biomarker Analysis[i]	X#				X		X	

STUDY PHASE	SCREENING	RANDOM-ISATION	BLINDED PHASE STUDY PERIOD				END OF BLINDED PHASE[u]	UNSCHEDULED VISIT[v]
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	NA
PROCEDURES	NA	NA	7-14 days after start of continuous treatment[t]-	3 months (±4 weeks) after randomisation	6 months (±4 weeks) after randomisation	9 months (±4 weeks) after randomisation	12 months (±4 weeks) after randomisation or within 4 weeks of withdrawal during blinded phase	NA
Pregnancy test[j]	X						X	
Ultrasound (Liver and Spleen)[k]	X#				X		X	
NPCCSS[l]	X#			X	X	X	X	X
NPC-cdb score[m]	X				X		X	
SARA[n]	X				X		X	
9HPT[n]	X				X		X	
CGI-S & CGI-I[n]	X			X	X	X	X	
Quality of Life Scoring[n]	X#				X		X	
Concomitant Therapy[o]	X							
Adverse Events[p]	X							
Randomisation		X						
IMP Dispensing		X$		X	X	X	X*	(X)
IMP Return[q]				X	X	X	X	(X)
IMP Administration[q]		X						
POP PK Sampling[r]				X	X	X	X	
Patient Acceptability/ Palatability[s]			X	X	X		X	
Telephone Follow up[w]			X (every month [±7 days])					

#The following assessments do not need to be repeated at Visit 1 if these assessments have been performed within 7 days of Visit 1: Physical examination including body weight and height, vital signs, ECG, skin punch biopsy, haematology, biochemistry, blood sample for biomarker analysis, ultrasound (liver and spleen), NPC Disease Severity Scores and Quality of Life scoring.

[a] **Demographics** includes date of birth, sex and race.

[b] **NPC diagnosis** based on date of initial symptom(s) and symptom(s) description, date of clinical diagnosis and symptoms clinical status, date of confirmed genetic NPC diagnosis, DNA sequence analysis and, if applicable, date of fillipin staining result and cholestane triol/oxysterols .

[c] **NPC disease history** including date of first NPC symptom, history of neurological manifestations and past treatments.

[d] **Physical examinations** during the study will include the assessment of skin, head, neck, lymphatic, abdomen, respiratory, cardiovascular/peripheral vascular, central nervous and musculoskeletal systems as appropriate to determine general condition.

[e] **Vital signs** will include supine blood pressure, pulse rate, respiratory rate and temperature (ear).

[f] A **twelve-lead ECG** will be recorded over at least 10 seconds after the patient has rested supine on a bed for at least 5 minutes.

[g] **Haematology** samples to be sent to a central laboratory for analysis.

[h] **Clinical chemistry** samples to be sent to a central laboratory for analysis.

[i] **Biomarker** samples to be sent to a central laboratory for analysis.

[j] Urine **pregnancy test** for post-menarchal female patients.

[k] **Ultrasound** of the liver and spleen to document changes in the size of the liver and spleen and any clinical relevant findings.

[l] **NPC clinical severity scale (NPCCSS)**: Refer to NPCCSS template provided for use in the study.

[m] **NPC-cdb score**: Refer to the modified NPC-cdb template provided for use in the study.

[n] **SARA**: Refer to SARA template provided for use in the study.

9HPT: Refer to 9HPT template provided for use in the study.

CGI-S & CGI-I: Refer to CGI-S and CGI-I templates provided for use in the study.

Quality of Life (EQ-5D-Y [Proxy version]) scoring will be completed by the patient's parent(s)/legal guardian(s).

[o] **Concomitant therapy** includes all medication and medical procedures (including any unplanned diagnostic, therapeutic or surgical procedures) ongoing at or starting after the time of written consent.

[p] **Adverse events (AEs)**: ALL AEs which are ongoing at Visit 1 and those that occur during study conduct, i.e. from the time of written informed consent to the end of the extension phase of the study or patient withdrawal, will be recorded in the eCRF.

[q] **IMP dispensing and administration**:

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

The patient's weight should be measured at each visit and the IMP dose should be adjusted as required and IMP dispensed as relevant.

During the blinded phase of the study, patients will be dispensed enough IMP for treatment as per the study flow chart.

[$]Confirmation of eligibility will be dependent on the availability of the relevant central lab results. In the event that confirmation of eligibility and subsequent randomisation of a patient occurs after the screening site visit, IMP (arimoclomol or placebo, as per the study randomisation) will be shipped to the patient, who will commence dosing upon receipt of it. The investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone within 1 week following randomisation to confirm that the IMP has been received, the date that the patient has commenced IMP dosing and whether the patient has experienced any difficulties in taking the IMP.

[*]The patient will be dispensed with sufficient arimoclomol at Visit 6 to continue treatment (for patients who have not withdrawn from the study).

Early Escape Criteria Met: Should a patient meet the early escape clause and criteria, the patient should be offered and dispensed treatment with arimoclomol. The patient should continue with their current protocol schedule.

IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty blister packs]) to the site staff. The site staff should aim to follow up on the reasons for any missing IMP or other discrepancies noted after performing the relevant IMP accountability.

r **POP PK Sampling**: POP PK sampling will be performed for all patients as follows:

- Visits 3 & 5: 3 hours (±1 hour) following dosing.
- Visits 4 & 6: 1.5 hours (±30 min), 3 hours (±30 min) and 4.5-6 hours following dosing. Note: The last POP PK sample should be taken as late as possible but always before the subsequent dose of IMP.

s **Patient Acceptability/Palatability**: Refer to the hedonic scale template provided for use in the study.

t **Visit 2** will take place 7-14 days after the patient has commenced taking the IMP t.i.d. (continuous treatment).

u **End of Blinded Phase (Visit 6)**: The end of blinded phase visit (Visit 6) should take place 12 months (±4 weeks) after randomisation or within 4 weeks of patient withdrawal during the blinded phase.

Withdrawal from study: Should a patient discontinue prematurely and choose to withdraw from the study during the blinded phase, all effort should be made to have the patient attend the site for the end of blinded phase visit (Visit 6) within 4 weeks of patient withdrawal. Should the patient (or the patient's parent[s]/legal guardian[s]) refuse to attend the end of blinded phase visit (Visit 6), the date and reason for study discontinuation (if known) will be recorded in the eCRF as a minimum.

v **Unscheduled visit**: The patient may attend the site for unscheduled visits should the patient experience an unacceptable rate of progression or should there be any safety concerns. IMP dispensing and return will take place in the event that a patient meets the early escape clause and criteria or a dose reduction has occurred.

w **Telephone follow up** to be performed every month (±7 days) for 6 months after the start of continuous treatment. Telephone follow-up includes follow-up on the status of the patient, whether the patient has experienced any new AEs or the worsening of any existing AEs, whether the patient has had a change in any prescribed medication, whether the patient has experienced any difficulties in taking the IMP and to confirm the weight of the patient.

16.1.3 Extension Phase Study Period: All Patients

STUDY PHASE	FOLLOW-UP			END OF EXTENSION PHASE[p]	UNSCHEDULED VISIT[o]
	Visit 7	Visit 8	Visit 9	Visit 10	NA
PROCEDURES	18 months (±4 weeks) after randomisation	24 months (±8 weeks) after randomisation	30 months (±8 weeks) after randomisation	36 months (±8 weeks) after randomisation or within 4 weeks of withdrawal during extension phase	NA
Physical examination[a]	X	X	X	X	
Weight	X	X	X	X	
Vital Signs[b]	X	X	X	X	
Haematology[c]	X	X	X	X	X
Clinical Chemistry[d]	X	X	X	X	X
Blood Sample for Biomarker Analysis[e]	X	X	X	X	
Pregnancy test[f]	X	X	X	X	
NPCCSS[g]	X	X	X	X	X
NPC-cdb score[h]	X	X	X	X	
SARA[i]	X	X	X	X	
9HPT[i]	X	X	X	X	
CGI-S & CGI-I[i]	X	X	X	X	
Quality of Life Scoring[i]	X	X	X	X	
Concomitant Therapy[j]	X	X	X	X	X
Adverse Events[k]	X	X	X	X	X
Arimoclomol Dispensing[l]	X	X	X		X
Arimoclomol Return[l]	X	X	X	X	X
Arimoclomol Administration[m]	X	X	X		X
Telephone Follow up[n]		X (every 3-4 months)			

[a] **Physical examinations** during the study will include the assessment of skin, head, neck, lymphatic, abdomen, respiratory, cardiovascular/peripheral vascular, central nervous and musculoskeletal systems as appropriate to determine general condition.

[b] **Vital signs** will include supine blood pressure, pulse rate, respiratory rate and temperature (ear).

[c] **Haematology** samples to be sent to a central laboratory for analysis.

[d] **Clinical chemistry** samples to be sent to a central laboratory for analysis.

[e] **Biomarker** samples to be sent to a central laboratory for analysis.

[f] Urine **pregnancy test** for post-menarchal female patients.

[g] **NPC clinical severity scale (NPCCSS)**: Refer to NPCCSS template provided for use in the study.

[h] **NPC-cdb score**: Refer to the modified NPC-cdb template provided for use in the study.

[i] **SARA**: Refer to SARA template provided for use in the study.

9HPT: Refer to 9HPT template provided for use in the study.

CGI-S & CGI-I: Refer to CGI-S and CGI-I templates provided for use in the study.

Quality of Life (EQ-5D-Y [Proxy version]) scoring will be completed by the patient's parent(s)/legal guardian(s).

[j] **Concomitant therapy** includes all medication and medical procedures (including any unplanned diagnostic, therapeutic or surgical procedures) ongoing at or starting after the time of written consent.

[k] **Adverse events (AEs)**: ALL AEs which are ongoing at Visit 1 and those that occur during study conduct, i.e. from the time of written informed consent to the end of the extension phase of the study or patient withdrawal, will be recorded in the eCRF.

[l] **Arimoclomol dispensing:** Patients will be dispensed sufficient arimoclomol to continue treatment. When this dispensing does not coincide with a site visit, this supply of arimoclomol will be shipped to the patient's home.

Arimoclomol return: Patients will be required to return all unused Arimoclomol (and relevant packaging [used/empty bottles]) to the site staff at each visit. The site staff should aim to follow up on the reasons for any missing Arimoclomol or other discrepancies noted after performing the relevant Arimoclomol accountability.

[m] **Arimoclomol administration**: If required, arimoclomol can be dissolved in 10 mL (i.e. 2 teaspoons) of liquid or in a tablespoon of soft foodstuff. In the dissolved or dispersed state, arimoclomol can also be administered via a gastric tube (as applicable).

The patient's weight should be measured at each visit and the arimoclomol dose should be adjusted as required and arimoclomol dispensed as relevant.

[n] **Telephone follow up** to be performed every 3-4 months following the start of the extension phase of the study. Telephone follow-up includes follow-up on the status of the patient, whether the patient has experienced any new AEs or the worsening of any existing AEs, whether the patient has had a change in any prescribed medication, whether the patient has experienced any difficulties in taking arimoclomol and to confirm the weight of the patient.

[o] **Unscheduled visit**: The patient may attend the site for unscheduled visits should the patient experience an unacceptable rate of progression or should there be any safety concerns.

- **End of Extension Phase**: The end of extension phase visit should take place within 36 months (±8 weeks) after randomisation or at the time of patient withdrawal from the study during the extension phase.

  Withdrawal from study: Should a patient discontinue prematurely and choose to withdraw from the study during the extension phase, all effort should be made to have the patient attend the site for the end of extension phase visit within 4 weeks of patient withdrawal. Should the patient (or the patient's parent[s]/legal guardian[s]) refuse to attend the end of extension phase visit, the date and reason for study discontinuation will be recorded in the eCRF as a minimum.