KemPharm Denmark A/S

CLINICAL STUDY PROTOCOL - CONFIDENTIAL

Protocol Number:	CT-ORZY-NPC-002
EudraCT Number:	2015-004438-93
IND Number:	124547
Title:	Arimoclomol prospective double-blind, randomised, placebo-controlled study in patients diagnosed with Niemann-Pick disease type C
Version and Date:	Final Version 11.0 – 21-Jun-2022
Sponsor:	KemPharm Denmark A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark
Clinicaltrials.gov ID:	NCT02612129

2. SIGNATURE PAGE

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

Sponsor

[redacted]

Chief Medical Officer

Tel: [redacted]

e-mail: [redacted]@KemPharm.com

[redacted]

Signature

28 June 2022

Date

Study Coordinating/Signatory Investigator:

Dr. med. [redacted]

Tel: +[redacted]

e-mail: [redacted]

[redacted]

Signature

28.06.2022

Date

3. PROTOCOL AGREEMENT PAGE

I confirm that I have read and that I understand this protocol, and all other information provided by KemPharm Denmark A/S.

I agree to conduct this study in conformity with this protocol and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the E6 International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), all applicable laws and regulations, including, without limitation, data privacy laws and regulations, and the regulatory requirements for reporting serious adverse events (SAEs) defined in Section 15.3 of this protocol.

Principal Investigator

Title and Name: .....

Hospital Name: .....

Signature: .....

Date: .....

4. SYNOPSIS

Study title:	Arimoclomol prospective double blind, randomised, placebo-controlled study in patients diagnosed with Niemann-Pick disease type C.
Protocol number:	CT-ORZY-NPC-002
Type of study:	Phase II/III
Sponsor:	KemPharm Denmark A/S
Principal Investigator:	Prof. Dr. med. [redacted]
Study centres:	15-20 sites in 6-9 countries
Laboratories	Central laboratories used for all samples: Clinical chemistry and haematology: Covance Indianapolis (United States sites); Covance Geneva (European sites). Biomarker analysis: Covance Harrogate, United Kingdom (cholesteryl esterification, oxysterol, unesterified cholesterol, heat shock protein 70 [HSP70]); KemPharm Denmark, Denmark (glycosphingolipids [GSLs], sphingoid bases); Centogene, Germany (LysoSM509).
Study design:	**MAIN STUDY:** A prospective, randomised, double-blind, placebo-controlled therapeutic study in patients with confirmed diagnosis of Niemann-Pick disease type C (NPC) on or not on miglustat therapy that either 1) have completed Visit 2 (end of study [EOS]) of the CT-ORZY-NPC-001 study or 2) meet the eligibility criteria of this study (CT-ORZY-NPC-001) including a requirement of stable treatment with miglustat for 6 months (if on miglustat therapy) prior to enrolment into CT-ORZY-NPC-002 study. It is anticipated that the majority of patients for inclusion in the CT-ORZY-NPC-002 study would have completed the CT-ORZY-NPC-001 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; each patient's standard of care may, or may not, include miglustat. Patients will be stratified into strata A (on miglustat therapy) and B (not on miglustat therapy). Hereafter, the patients will be randomised to receive placebo or arimoclomol (with an allocation ratio of 1:2). To confirm the selected dose, patients less than 12 years of age will undergo an arimoclomol single-dose pharmacokinetic (PK) evaluation before randomisation and the start of continuous (multiple dosing) treatment. The duration of the blinded phase study period will be 12 months. Following this, all patients will be offered to continue into the extension phase of the study where every patient will receive arimoclomol and attend site visits at 18 months, and every 6 months thereafter until End of Extension Phase at 60 months (after patient randomisation). The extension phase runs for 48 months or until arimoclomol has received European Union (EU)/United States (US) marketing authorisation (MA) or until the analysis of data from the controlled, blinded phase 12-month 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 (amendment to protocol). Patients will be enrolled in the extension phase only if the investigator deems that the patient is deriving clinical benefits from the trial participation. The Investigator will contact the patient (or the patient's parent[s]/legal guardian[s]) by telephone (monthly calls during the first 6 months of the blinded phase and every 3-4 months following the start of the extension phase) to 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 investigational medicinal product (IMP) and to confirm the weight of the patient. Should the patient experience disease progression that is too severe and/or too fast or should there be any safety concerns, the patient may also attend the site for unscheduled visits. In order to perform an exploratory exposure-response analysis, sampling for Population Pharmacokinetics (POP PK) of arimoclomol and metabolites (if relevant) will be performed in all patients at Visits 3, 4, 5, and 6 (3, 6, 9 and 12 months respectively). A Data Safety Monitoring Board (DSMB) will review the safety data during the blinded phase of the study. Should a patient discontinue prematurely and choose to withdraw from the study, all effort should be made to have the patient attend the site for a withdrawal visit during the blinded or the extension phase of the study (depending on the time point of withdrawal). In patients whose disease progression is too severe and/or too fast, the "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. **Early Escape Clause and Criteria:** The "early escape clause" can be invoked when a set of criteria are met in the event that a participating patient experiences disease progression that is too severe and/or too fast. In such cases, the patient will: 1) Stop receiving the IMP; 2) Be offered treatment with arimoclomol; 3) Continue with their current protocol schedule. For evaluation of a potential early escape, the three relevant domains of the NPC Clinical Severity Scale (NPCCSS) to be assessed are: Ambulation, Swallowing and Fine Motor Skills. The investigator will assess the following criteria to determine if the "early-escape clause" is to be invoked for the particular patient: **EITHER** • <u>Criterion 1:</u> An increase of at least 2 points simultaneously in two out of the three relevant domains of the NPCCSS (for at least 4 points in total) within a period of 3 months; **OR**

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

OR

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

The Investigator will submit all requests for early escape to Worldwide Clinical Trials for review and approval.

Following the review of relevant juvenile toxicology data and PK information from 100% of the patients aged 2 to <12 years, the CT-ORZY-NPC-002 study has now been expanded to include a paediatric substudy in patients aged 6 to <24 months at study enrolment which will assess the safety and tolerability of 36 months of open-label arimoclomol when it is administered as an add-on therapy to the patient's current prescribed best standard of care; each patient's standard of care may, or may not, include miglustat. Data from the paediatric substudy will be analysed and reported separately from the data in the main study.

PAEDIATRIC SUBSTUDY:

[redacted]

Study objectives:	**MAIN STUDY:** **Primary:** • To evaluate therapeutic response to arimoclomol versus placebo, both in addition to best available standard of care, at 12 months. **Secondary:** • To evaluate the therapeutic response to arimoclomol through clinical, biological and imaging assessments at 6 and 12 months; • To evaluate the long-term therapeutic response (clinical and biological assessments) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • To evaluate the safety of arimoclomol. **PAEDIATRIC SUBSTUDY:** [redacted]
Study drug and dosage form:	**MAIN STUDY:** **Blinded Phase Study Period** Arimoclomol citrate or placebo in hard capsules of 25 mg, 50 mg, and 100 mg, which are supplied either in single-dose high density polyethylene (HDPE) bottles for the initial single dose PK evaluation (patients less than 12 years of age only), or supplied in blister packages mounted within wallets which are packaged within a box for the placebo-controlled part. **Extension Phase** Arimoclomol citrate in hard capsules of 25 mg and/or 50 mg and/or 100 mg are supplied in HDPE bottles. **PAEDIATRIC SUBSTUDY:** [redacted]
Doses to be studied:	**MAIN STUDY:** Dosing is based on the patient's body weight (BW):

Patient Body Weight	Arimoclomol Citrate 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 and the IMP dose is to be adjusted as required. In the event that a patient who is receiving 150 mg IMP per day requires a dose reduction, then a dose of 75 mg per day (25 mg t.i.d) should be administered. For individual patients less than 12 years of age, to confirm the corresponding dose, a single dose PK evaluation will be performed by an independent assessor following a single dose of arimoclomol to verify the area under the curve in 0-8 hours (AUC_{0-8}). In the event that patients require a dose reduction, these patients will be dispensed a further single dose of arimoclomol, and a new single dose PK evaluation will be performed to confirm the corresponding dose. Should further dose adjustments be required, based on the second single dose PK evaluation, the above procedure will be repeated until the correct dose level is found. Also, in the event that unexpected PK-profiles are obtained (from patients less than 12 years of age) which are clinical significant and could potentially impact the safety of the patient, the independent assessor can recommend additional PK sampling to be performed (in agreement with the Sponsor's medical responsible person and the Principal Investigator). The results of this analysis might lead to dose adjustments as recommended by the independent assessor. This/these dose reduction(s) will take place prior to randomisation and to commencing continuous dosing of IMP (arimoclomol or placebo, as per the study randomisation). **PAEDIATRIC SUBSTUDY:** [redacted]
Dosing route and regimen	**MAIN STUDY:** IMP (arimoclomol or placebo) will be administered orally t.i.d. If required, the IMP can be dispersed in 10-20 mL (i.e. 1-2 tablespoons) of liquid (water, apple juice) or soft foodstuff (yoghurt or apple sauce). In the dispersed state, the IMP capsules can also be administered via a gastric tube (as applicable). For full administration of the dose, flush the tube with 5 mL of water. **PAEDIATRIC SUBSTUDY:** [redacted]

	[redacted]
Dose adjustment:	**MAIN STUDY:** Patients less than 12 years of age may have their dose adjusted (decrease) following a single oral dose of arimoclomol based on review of the following criteria by an independent assessor: • AUC_{0-8} Also, in the event that unexpected PK-profiles are obtained (from patients less than 12 years of age) which are clinical significant and could potentially impact the safety of the patient, the independent assessor can recommend additional PK sampling to be performed (in agreement with the Sponsor's medical responsible person and the Principal Investigator). The results of this analysis might lead to dose adjustments as recommended by the independent assessor. In addition to this, a patient who has commenced continuous dosing with the IMP is to be considered for dose reduction should the following criteria be met: • Serum creatinine above 1.5 x the patient's baseline creatinine value. Dose adjustment may be temporary however, subsequent dose increase must be discussed with the KemPharm Denmark's medical monitor (or delegate); **Note**: Serum creatinine calculation = Serum creatinine value/baseline serum creatinine value. Result rounded to 1 decimal point as per normal rounding principles. • Decrease in the patient's weight (as confirmed during a site visit) meeting the lower weight range in the actual dose group. Administration of IMP will be stopped and the patient withdrawn from the study should the following criteria be met: • CTCAE* Grade 2 acute kidney injury considered related to the IMP (which corresponds to the serum creatinine increase of above 2-3 x the patient's baseline creatinine value);

Note: Serum creatinine calculation = Serum creatinine value/baseline serum creatinine value. Result rounded to 1 decimal point as per normal rounding principles.

- CTCAE* Grade 3 hepatic related parameters (aspartate transaminase [AST] and/or alanine transaminase [ALT]) considered related to the IMP;
- Other CTCAE* Grade 3 AEs considered related to the IMP.

**National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.*

The individual patient dose will be adapted if required upon patient's weight changes at every visit.

PAEDIATRIC SUBSTUDY:

[redacted]

	[redacted]
Study population:	**MAIN STUDY:** Male and female patients with a confirmed diagnosis of NPC1 or NPC2 on or not on miglustat therapy that either 1) have completed Visit 2 (EOS) of the CT-ORZY-NPC-001 study or 2) meet the eligibility criteria of this study (CT-ORZY-NPC-001) including a requirement of stable treatment with miglustat for 6 months (if on miglustat therapy) prior to enrolment into CT-ORZY-NPC-002 study. It is anticipated that the majority of patients for inclusion in the CT-ORZY-NPC-002 study would have completed the CT-ORZY-NPC-001 study. **PAEDIATRIC SUBSTUDY:** [redacted]
Diagnosis and main criteria for inclusion:	**Main inclusion criteria:** • Diagnosis of NPC1 or NPC2; • NPC diagnosis confirmed by: Genetically confirmed (deoxyribonucleic acid [DNA] sequence analysis) by mutations in both alleles of NPC1 or NPC2, OR o Mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane triol/oxysterols (>2 x upper limit of normal [ULN]). • Main study: Males and females aged from 2 years to 18 years and 11 months; • Paediatric substudy: [redacted] • Treated or not treated with miglustat; o Main study: If a patient is under prescribed treatment with miglustat, it has to be under stable dose of the medication for at least 6 continuous months prior to inclusion in the CT-ORZY-NPC-002 study; o Main study: If a patient has been discontinued from prescribed treatment with miglustat, they must have been discontinued for at least 3 continuous months prior to inclusion in the CT-ORZY-NPC-002 study; o Paediatric substudy: [redacted]

	○ Paediatric substudy: [redacted] **Main exclusion criteria:** • Severe liver insufficiency (defined as hepatic laboratory parameters, AST and/or ALT greater than three-times the ULN for age and gender [central laboratory assessment]); • Renal insufficiency, with serum creatinine level greater than 1.5 times the ULN (central laboratory assessment); • Paediatric substudy: [redacted] • Paediatric substudy: [redacted] • Paediatric substudy: [redacted] • Paediatric substudy: [redacted]
Number of planned visits:	**MAIN STUDY:** The trial includes the following visits: • Visit 1 (Site): ○ Screening; ○ PK to confirm doses for patients less than 12 years of age; ○ Additional PK visits (site) for patients less than 12 years of age if required; ○ Randomisation. • Blinded Phase: ○ Telephone follow up every month (±7 days) for 6 months after the start of continuous treatment; ○ Visit 2 (site): 7-14 days after the start of continuous treatment; ○ Visit 3 (site): 3 months (±4 weeks) after patient randomisation; ○ Visit 4 (site): 6 months (±4 weeks) after patient randomisation; ○ Visit 5 (site): 9 months (±4 weeks) after patient randomisation; ○ Visit 6 (site)/End of Blinded Phase: 12 months (±4 weeks) after patient randomisation or at patient withdrawal during the blinded phase. Visits 2 through 6 will include scoring for disease severity, blood and skin biopsy sampling for biomarkers, as well as assessment of safety, compliance, Scale for Assessment and Rating of Ataxia (SARA), Nine-hole Peg Test (9HPT), Clinical Global Impression Scale – Severity (CGI-S), Clinical Global Impression Scale - Improvement (CGI-I) and Quality of Life. • Extension Phase:

- Visit 7 (site): 18 months (±4 weeks) after patient randomisation;
- Visit 8 (site): 24 months (±8 weeks) after patient randomisation;
- Visit 9 (site): 30 months (±8 weeks) after patient randomisation;
- Visit 10 (site): 36 months (±8 weeks) after patient randomisation;
- Visit 11 (site): 42 months (±8 weeks) after patient randomisation;
- Visit 12 (site): 48 months (±8 weeks) after patient randomisation;
- Visit 13 (site): 54 months (±8 weeks) after patient randomisation;
- Visit 14 (site)/End of Extension Phase: 60 months (±8 weeks) after patient randomisation or at patient withdrawal during the extension phase.

  Visits 7 to 14 will include scoring for disease severity, blood sampling for biomarkers, as well as assessment of safety, compliance, SARA, 9HPT, CGI-S, CGI-I and Quality of Life;
- Telephone follow up every 3-4 months.

PAEDIATRIC SUBSTUDY:

[redacted]

	[redacted]
Total sample size:	**MAIN STUDY:** Up to fifty-two (52) patients will be randomised in the study as the final target is to have at least forty (40) evaluable patients (at least 30 of these should be paediatric patients less than 18 years of age). **PAEDIATRIC SUBSTUDY:** [redacted]
Primary endpoint:	**MAIN STUDY:** • 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;
Clinical status endpoints:	**MAIN STUDY:** Key Secondary Endpoints: • Responder analysis of patient's CGI-I score remains stable or shows improvement at 12 months (for the United States Food and Drug Administration [FDA] submission, this endpoint is considered co-primary); • Responder analysis of patient's 5 domain NPCCSS score remains stable or improves at 12 months compared to baseline; • Time to worsening (as defined by reaching the minimal clinically important difference [MCID] 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 score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 12 months. Other Secondary Endpoints: • Change in 5 domain NPCCSS score at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Responder analysis of the CGI-I score remains stable or shows improvement at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Responder analysis of 5 domain NPCCSS score remains stable or improves at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months compared to baseline; • Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Changes in each individual domain of the NPCCSS at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;

	• Change in the Niemann Pick type C Clinical Database (NPC-cdb) score (modified "Stampfer Score" [Stampfer et al., 2013]) at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Change in Quality of Life (EQ-5D-Y) at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Change in the SARA score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • Change in the 9HPT time at 6, 12 and 18 months, and every 6 months thereafter until End of Extension Phase at 60 months; • CGI-S score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months; • CGI-I score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months. **PAEDIATRIC SUBSTUDY:** • [redacted]
Exploratory Endpoints	**MAIN STUDY:** • 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 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months.
Safety endpoints:	**MAIN STUDY AND PAEDIATRIC SUBSTUDY:** • Adverse events (AEs); • Haematology; • Clinical chemistry; • Vital signs;
Imaging endpoints:	**MAIN STUDY:** • Changes in the size of the liver and spleen (assessed by ultrasound). Changes at 6 and 12 months. **PAEDIATRIC SUBSTUDY:** • [redacted]
Biomarker endpoints:	**MAIN STUDY:** • NPC1 active protein; • NPC1 protein function (cholesteryl esterification); • Oxysterol (cholestane-3β,5α,6β-triol); • Un-esterified cholesterol;

	• HSP70; • GSLs; • Sphingoid bases; • Lyso-SM-509. Changes at 6 and 12 months (placebo versus arimoclomol) will be evaluated. During the extension phase of the study, the following biomarkers will be analysed: • Oxysterol (cholestane-3β,5α,6β-triol); • Un-esterified cholesterol; • HSP70; • GSLs; • Lyso-SM-509. **PAEDIATRIC SUBSTUDY:** • [redacted]
Other endpoints:	**MAIN STUDY:** • Patient acceptability/palatability of the IMP (blinded phase study period).
Statistical methods:	Descriptive analyses will be performed. Data will be summarised as follows: Continuous variables by descriptive statistics (number of patients [N], mean, SD, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %). Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed for reporting summary statistics. If a baseline value is missing, no change from baseline will be calculated. **MAIN STUDY:** **Evaluation of Primary Endpoint:** The primary analysis is by a general linear mixed model for repeated measurements. The primary endpoint is 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 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 model allows for the calculation of the 95% confidence interval (CI) for the treatment effect, and a *P*-value to test the null hypothesis that the effect of arimoclomol and placebo is the same. **Evaluation of Secondary Endpoints:** <u>Key Secondary Endpoints</u>: • *Responder analysis of patient's CGI-I score remains stable or shows improvement at 12 months and descriptive summary of responder rate at 12 months (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 and descriptive summary of responder rate at 12 months*. These will be analysed at 12 months using two-tailed chi-squared tests. 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. • *Time to worsening (as defined by reaching the MCID in patient's 5 domain NPCCSS)* Kaplan-Meier plots for time to worsening will be produced for each treatment group and compared via a log-rank test, stratified for use of miglustat. • *Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 6 and 12 months* This will be analysed using two-tailed chi-squared tests. 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. • *Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) from baseline to 12 months*: This will be analysed using an analysis of covariance model including baseline full scale NPCCSS score (apart from hearing domains), miglustat and randomised treatment as the only covariates.

	Other Secondary Endpoints: • *Change in 5 domain NPCCSS at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* The change in 5 domain NPCCSS at 6 months will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months. Data from 18 months and beyond will be summarised descriptively. • *Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months*: This will be analysed descriptively. • *Responder analysis of the CGI-I score remains stable or shows improvement at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months.* • *Responder analysis of 5 domain NPCCSS score remains stable or improves at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months compared to baseline*. • *Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months*. • *Changes in each individual domain of the NPCCSS at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* These will be tabulated and presented descriptively, including each domain score and its change from baseline. • *Change in the NPC-cdb score (modified "Stampfer Score") at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months. • *Change in Quality of Life (EQ 5D Y) at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* The changes from baseline will be simply compared by a Mann Whitney (independent samples) test and 95% CI at each of 6 and 12 months). Data from 18 months and every 6 months thereafter until End of Extension Phase at 60 months will be summarised descriptively. • *Change in the SARA score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the NPCCSS (apart from hearing domains) at 6 months. • *Change in the 9HPT time at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the NPCCSS (apart from hearing domains) at 6 months. • *CGI-S score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed descriptively showing the distribution of scores for each treatment group at 6 and 12 months and the overall distribution of scores at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

- *CGI-I score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed descriptively showing the distribution of scores for each treatment group at 6 and 12 months and the overall distribution of scores at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

Evaluation of Exploratory Endpoints:

- *NPC disease progression rate based on the NPCCSS (apart from hearing domains) from baseline in the CT-ORZY-NPC-002 study to 6 and 12 months.* This will be analysed using a similar model as for the change in the NPCCSS score at 6 months. Specifically, the analysis of covariance models (2 models) will have as response variables: rate of disease progression between Baseline and (1) 6 months in the *CT-ORZY-NPC-002* study and (2) 12 months in the *CT-ORZY-NPC-002* study. The covariates in each model (the same in both analyses) will be rate of disease progression in study CT-ORZY-NPC-001, miglustat use, and randomised treatment.
- *The number of patients leaving the blinded phase of the study before 12 months as a result of early escape* will be presented.
- *The number of patients who either withdraw from the study before 12 months, or who need to jump to escape therapy* will be presented.
- *Change in use of NPC medication/standard of care (including miglustat therapy) at 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months* will be listed.

Subgroup Analyses:

Exploratory subgroup analyses will be performed on the primary and three 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. Exploratory subgroup analyses will be performed based upon:

- 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) at baseline divided into tertiles; 0 - ≤18, 19 - ≤36, 37 - ≤54);
- Change in full scale NPCCSS score (apart from hearing domains) from baseline to 3 months for patients with late infantile phenotype (age at the start of neurological symptoms: 2 to <6 years).

	PAEDIATRIC SUBSTUDY: [redacted]

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ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
API	Active Pharmaceutical Ingredient
AST	Aspartate Transaminase
AUC	Area under the Curve
AUC_{0-8}	Area under the Curve in 0-8 hours
$AUC_{0-8,SS}$	Area under the Curve in 0-8 hours at Steady State
AUC_{0-24}	Area under the Curve in 0-24 hours
AUC_{tau}	Area under the Curve over the Dosing Interval at Steady State
BBB	Blood Brain Barrier
BMI	Body Mass Index
BW	Body Weight
CAS	Completers Analysis Set
CFS	Cerebrospinal Fluid
CGI-I	Clinical Global Impression Scale – Improvement
CGI-S	Clinical Global Impression Scale – Severity
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance

CL/F	Oral Clearance
C_{max}	Peak Serum Concentration
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT (Module)	Clinical Trials (Module)
CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA/EMEA	European Medicines Agency
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GSL	Glycosphingolipid
HDL	High-density Lipoprotein
HDPE	High Density Polyethylene
HPMC	Hydroxypropyl Methylcellulose

9HPT	Nine-hole Peg Test
HSP	Heat Shock Protein
HSP70	Heat Shock Protein 70
HSR	Heat Shock Response
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
LAR	Legal Authorised Representative
LDH	Lactate Dehydrogenase
LDL	Low-density Lipoprotein
LSD	Lysosomal Storage Disorder
MA	Marketing Authorisation
MAR	Missing at Random
[redacted]	[redacted]
MCID	Minimal Clinically Important Difference
NOEL	No Observed Effect Level
NPC	Niemann-Pick Disease Type C
NPCCSS	NPC Clinical Severity Scale
NPC-cdb	Niemann-Pick Type C Clinical Database
PBMC	Peripheral Blood Mononuclear Cell

PICD	Patient Informed Consent Document
PK	Pharmacokinetic
POP PK	Population Pharmacokinetic
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARA	Scale for Assessment and Rating of Ataxia
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d.	Three Times a Day
T_{max}	Time to Peak Serum Concentration
ULN	Upper Limit of Normal
US/USA	United States/United States of America
WBC	White Blood Cell
WHO	World Health Organisation

7. INTRODUCTION

7.1. NIEMANN-PICK DISEASE TYPE C

Niemann-Pick disease type C (NPC) is a very rare, fatal, neurovisceral, atypical lysosomal storage disorder (LSD) presenting impaired cellular functions in processing and transporting low-density lipoprotein-cholesterol (Huang et al., 2011). The disease affects all organs and it is characterised by a significant variety of progressive and disabling neurological symptoms (Vanier, 2010). NPC presents an extremely heterogeneous clinical manifestation which progresses over varied periods of time (Imrie et al., 2007; Patterson et al., 2012).

The estimated incidence is 1:150,000 live births (Wraith et al., 2009) or 0.1 in 10,000 people in the European Union (EU).

NPC is transmitted in an autosomal recessive manner and is caused by mutations of either the NPC1 (95% of families) or the NPC2 genes (in approximately 5% of cases). Patients with NPC1 or NPC2 mutations are not clinically distinguishable. Undetected causal gene mutations may also exist.

The broad clinical spectrum ranges from a neonatal rapidly fatal disorder to an adult onset chronic neurodegenerative disease. The neurological involvement defines the disease severity in most patients but is typically preceded by systemic signs (cholestatic jaundice in the neonatal period or isolated spleno- or hepatosplenomegaly in infancy or childhood).

The disease progression largely correlates with the age at onset of the neurologic symptoms.

Progressive neurological disease is the hallmark of NPC, and is responsible for disability and premature death in all cases. Classically, children with NPC may initially present with delays in reaching normal developmental milestones before manifesting cognitive decline and dementia.

Neurological signs and symptoms include cerebellar ataxia, dysarthria, dysphagia, tremor, epilepsy (both partial and generalized), vertical supranuclear palsy (up gaze palsy, down gaze palsy, saccadic palsy or paralysis), sleep inversion, gelastic cataplexy, dystonia, spasticity, hypotonia, ptosis, microcephaly, psychosis, progressive dementia, progressive hearing loss, bipolar disorder, major and psychotic depression that can include hallucinations, delusions, mutism, or stupor.

In the terminal stages of NPC, the patient is bedridden, with complete ophtalmoplegia, loss of volitional movement and severe dementia.

7.2. ARIMOCLOMOL

Arimoclomol acts as a co-inducer of heat shock protein 70 (HSP 70, a major component of the so-called heat shock response [HSR]) under conditions of cellular stress. The HSR has been established as therapeutic target in LSDs in several studies.

Several previous studies have established the HSR as therapeutic target in NPC. In a recent study, HSP70 was shown to be critical for the proper folding and activity of the NPC1 protein, which is mutated in the majority of patients with NPC. Importantly, this study furthermore demonstrated that induction of HSP70 can rescue the most common genetic defect in the NPC1 protein and the resulting cellular pathology.

Proof-of-concept for the use of arimoclomol has been established *in vitro* and *in vivo*, in a mouse model of disease. In the $NPC1^{-/-}$ mouse model, arimoclomol was effective in improving neurological symptoms and reducing the accumulation of glycosphingolipids (GSLs) which is a pathobiochemical hallmark of NPC. These results strongly suggest that arimoclomol may confer similar benefits to patients with NPC. Refer to the Investigator Brochure (IB) for further information.

7.2.1. Clinical Data

Clinical experience on arimoclomol originates from 7 Phase I studies and 2 Phase II studies in Amyotrophic Lateral Sclerosis (ALS) patients. Phase I studies with arimoclomol include a single-dose study, a multiple-dose study, an ascending multiple-dose study, two food effect studies, a mass balance study to determine absorption, distribution, metabolism, elimination (ADME), and a renal safety study. In addition, pharmacokinetic (PK) parameters were assessed in one of the Phase II studies in ALS patients.

Overall, arimoclomol was absorbed rapidly and arimoclomol exposure (based on peak serum concentration [C_{max}] and are under the curve [AUC]) has been shown to increase in a nearly dose proportional manner.

Steady state appeared to have been reached by 24 hours after the start of three times a day (t.i.d.) dosing for all dose levels.

Across all clinical studies performed (including the Phase II studies in ALS patients) an average $t_{1/2}$ of 3.5 hours and a time to peak serum concentration (T_{max}) of 1-2 hours has been found.

Furthermore, the food effect was evaluated in 2 studies (single dose administration of 100 mg and 400 mg arimoclomol citrate). No food effect (based upon AUC and C_{max}) was observed following the administration of arimoclomol in the fed compared to the fasted state.

To date, a total of 106 healthy subjects received arimoclomol citrate at doses ranging from 50 mg (single dose) to 1800 mg (600 mg dosed t.i.d.).

In the Phase II study (Study AALS-001), 62 patients with ALS were administered 25-100 mg arimoclomol citrate t.i.d. for 3 months. A total of 69 patients from this study (previously treated with arimoclomol or placebo) continued in the open-label extension study (Study AALS-001-OL), receiving 100 mg arimoclomol citrate t.i.d. for an additional 6 months.

In summary, safety data from the Phase I studies and the Phase II studies in ALS patients suggest that arimoclomol may lead to a drug-related increase in serum creatinine, and a decrease in mean creatinine clearance. All observed changes in creatinine were reversible. Since there was no change in glomerular filtration rate and serum cystatin C, this suggests an inhibitory effect of arimoclomol on tubular secretion of creatinine.

In an *in vitro* transporter study, arimoclomol was shown to be an inhibitor of OCT2 transporter (with initial inhibitory activity of this transporter at C_{max} of individual human doses higher than 400 mg). OTC2 transports creatinine; thus, inhibition of this transporter could provide an explanation for the modest increases in serum creatinine found in clinical studies.

Other adverse events (AEs) related to arimoclomol were gastrointestinal disorders (diarrhoea being most frequently reported) as well as dry mouth (this was the most frequently treatment related AE reported in the ALS studies).

Refer to the IB for more information.

7.3. RATIONALE FOR THE STUDY AND RISK-BENEFIT ASSESSMENT

NPC is an extremely rare, progressive and life-threatening disease. The clinical manifestation regarding symptoms, severity and progression is very heterogeneous amongst patients. There is no approved cure for NPC. In the absence of any curative treatment for NPC, quality of life represents the treatment goal in the management of the patients, and can be addressed by (Patterson et al., 2012):

- Rigorous symptomatic treatment
- Miglustat therapy for existing neurological manifestations

Symptomatic treatments are targeting:

- Neurological manifestations: such as seizures, cataplexy, dystonia and tremor, dysphagia, drooling and sleep disturbances
- Cognitive impairment
- Psychiatric illness
- Systemic manifestations

In Europe, miglustat was approved in 2010 as disease modifying therapy for the treatment of progressive neurological symptoms in NPC patients. Miglustat reduces substrate load, intended to slow down the progressive neurological manifestations in adult and paediatric NPC patients. The available data on miglustat support that at least some patients might benefit from treatment in that the progression of disease is slowed down. The benefit of the treatment should be evaluated on regular basis, e.g. every 6 months to monitor potential or expected AEs and the continuation of the therapy should be re-appraised after at least 1 year of treatment with miglustat.

Several previous studies have established the HSR as therapeutic target in LSDs (Ingemann and Kirkegaard, 2014). The HSR is a key homeostatic system, which is induced under conditions of metabolic stress (e.g. protein misfolding and aggregation, nutrient deprivation, oxidative or thermal stress). Its main components are the heat shock proteins (HSPs), in particular HSP70, which have significant cytoprotective properties. HSP70 act as molecular chaperone, assisting in the folding of newly synthesized or damaged proteins, preventing protein aggregation, and targeting severely damaged proteins for degradation. Notably, the cytoprotective actions of HSP70 also include protection against lysosomal dysfunction and cell death (Ingemann and Kirkegaard, 2014).

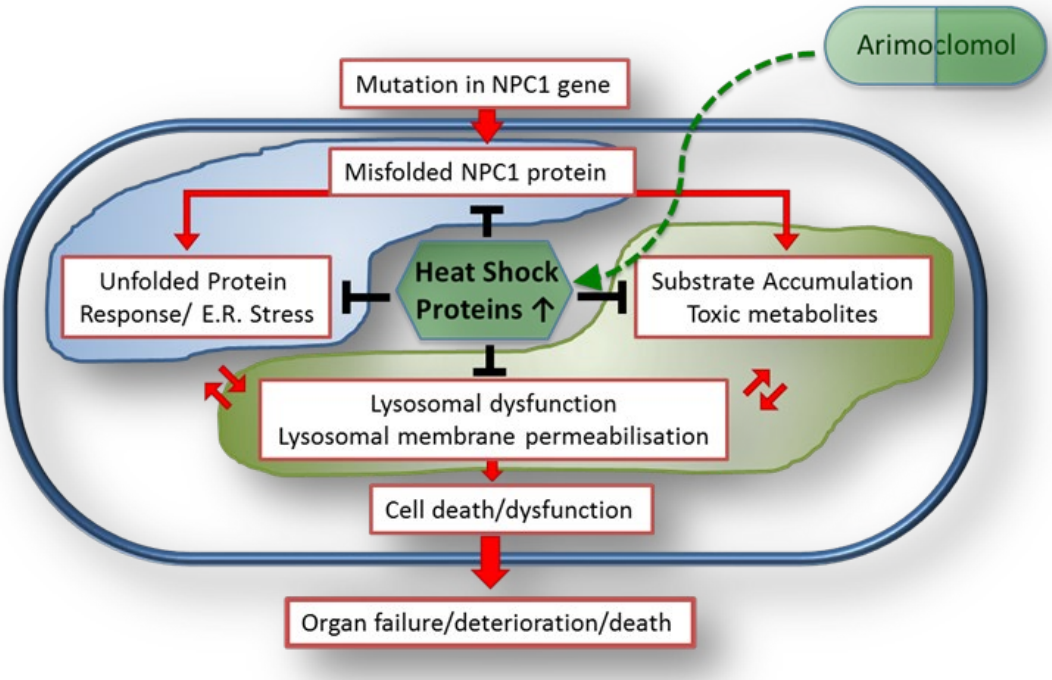
Since most LSDs are characterized by lysosomal dysfunction, cell death and significantly reduced enzyme activity due to missense mutations rather than complete loss of function, the LSDs are amenable to therapeutic approaches involving HSP70 (Kirkegaard, 2013; Ingemann and Kirkegaard, 2014).

Arimoclomol is a co-inducer of HSP70 expression which acts through the activation of heat shock factor-1 (HSF-1), the major regulator of HSP gene transcription (Neef et al., 2011).

Through the induction of HSP70-proteins, arimoclomol aids the proper folding of otherwise misfolded NPC1 protein, hereby correcting the root cause of NPC disease (Figure 7-1). Additionally, HSP70 proteins improve lysosomal function, a key target in NPC disease. The molecular actions of arimoclomol thus correct several aspects of the molecular pathology of NPC disease in a concerted action, providing the mechanistic rationale for the hypothesized therapeutic benefit of arimoclomol in NPC patients.

Another aspect related to the therapeutic potential of arimoclomol is its ability to cross the blood brain barrier (BBB). By penetration into the central nervous system (CNS) arimoclomol is suggested to bring direct neurologic benefit also to the NPC phenotype.

Figure 7-1: Proposed Mechanism of Arimoclomol of Ameliorating Niemann-Pick Disease Type C Disease



The observational (non-therapeutic, interventional) study, CT-ORZY-NPC-001 was designed to better characterise the individual patient disease profile (disease burden) through the clinical, imaging, biological status, and Quality of Life prospectively recorded, together with the historic disease information collected from patient medical records. It also allowed the evaluation of the safety data of the disease-related therapy and to record every AE linked to the disease. The study was categorized as interventional due to the nature and frequency of the study procedures, which are not necessarily performed as a standard of care.

During the study CT-ORZY-NPC-001, the patients remained on their prescribed disease related therapy (based on the choice of their treating physician) and did not receive any investigational medicinal product (IMP). All patient-care decisions, including diagnostic and therapeutic interventions, were made by and conducted at the discretion of the Investigators according to their clinical judgement and the local standard of medical care.

The only standard of care limitation was that miglustat therapy was to be stable for at least 6 months before study participation (for those patients in treatment with miglustat), and that patients with three or more anticonvulsants were excluded from participation. For those patients who had been discontinued from prescribed treatment with miglustat, they must have been discontinued for at least 3 continuous months prior to inclusion in the study.

The procedures performed in the study CT-ORZY-NPC-001 are the same that the ones which will be carried out in study CT-ORZY-NPC-002, apart from the Scale for Assessment and Rating of Ataxia (SARA), Nine-hole Peg Test (9HPT), Clinical Global Impression Scale – Severity (CGI-S), Clinical Global Impression Scale - Improvement (CGI-I), PK, Population Pharmacokinetics (POP PK) and IMP related procedures which are exclusively performed in study CT-ORZY-NPC-002. The addition of the SARA, 9HPT, CGI-S and CGI-I will not add any burden to the study patients.

Following on from the CT-ORZY-NPC-001 observational study, this Phase II/III interventional therapeutic study (CT-ORZY-NPC-002) will assess the efficacy and safety of arimoclomol (compared to placebo). This study will allow for a thorough evaluation of the clinical (NPC Clinical Severity Scale [NPCCSS], NPC Clinical Database [NPC-cdb], SARA, 9HPT, Quality of Life, CGI-S and CGI-I), biological/biochemical (unesterified cholesterol, oxysterol, HSP70, NPC1 protein, GSLs and sphingoid bases), POP PK and imaging (ultrasound of liver and spleen) markers in a randomised controlled setting ensuring the generation of reliable data for the assessment of therapeutic response of arimoclomol.

In the CT-ORZY-NPC-002 study, the IMP (arimoclomol or placebo) will be administered orally t.i.d. as an add-on therapy to the patient's current prescribed best standard of care. The duration of the controlled blinded phase study period will be 12 months; following this period, every patient will continue into the extension stage of the study where they will receive arimoclomol in addition to the best standard of care and be followed up at 18 months and every 6 months thereafter until End of Extension Phase at 60 months (after patient randomisation). The extension phase runs for 48 months or until arimoclomol has received 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 (amendment to protocol).

Following the review of relevant juvenile toxicology data and PK information from 100% of the patients aged 2 to <12 years, the CT-ORZY-NPC-002 study has now been expanded to include a paediatric substudy in patients aged 6 to <24 months at study enrolment which will assess the safety and tolerability of 36 months of open-label arimoclomol when it is administered as an add-on therapy to the patient's current prescribed best standard of care; each patient's standard of care may, or may not, include miglustat (refer to APPENDIX V: Paediatric Substudy for description of the substudy).

Arimoclomol has been shown to be well tolerated in healthy subjects and ALS patients. To date, a total of 106 healthy subjects have received arimoclomol citrate at doses ranging from 50 mg (single dose) to 1800 mg (600 mg dosed t.i.d.) and a total of 69 ALS patients have received 100 mg arimoclomol citrate t.i.d. for at least 6 months with no safety concerns.

Refer to Section 11.2.1 for the rationale behind the dose recommendations for the CT-ORZY-NPC-002 study.

The potential risks involved in this study concern those routinely linked to the interventional study procedures of skin punch biopsy procedure and blood draws for clinical haematology, biochemistry and biomarkers, and venous blood samples for the PK analysis (in patients less than 12 years of age) and POP PK analysis in all patients.

One of the key requirements of a clinical trial is to assess as early and as reliable as possible any consistent pharmacodynamics effect of the drug being tested. KemPharm Denmark A/S decided to perform in the participating NPC patients in this study, the least invasive and best researched tissue (skin biopsy and blood sampling) instead of more invasive sampling assessment of cerebrospinal fluid (CFS) or the biopsy of other organs for this study. Skin biopsies are therefore required in this study to assess the effect of arimoclomol on lysosomal lipid sequestration as well as NPC1 protein expression.

The key component of NPC disease is the sequestration of cholesterol and GSLs in the lysosomes. For this reason, Filipin staining of cultured fibroblast from skin biopsies is used as a diagnostic tool to confirm the accumulation of un-esterified cholesterol prior to sequencing of the NPC gene (Vanier, 2010). Likewise, the characterization of the NPC1 protein function and post translational glycosylation have been addressed in primary fibroblast cell cultures, which also show increased GSL accumulation (Gelsthorpe et al., 2008) (Sun et al., 2001; Watanabe et al., 1998; Yu et al., 2012; Zampieri et al., 2012). Therefore, the purpose of the skin punch biopsies is not to generate fibroblast cultures, but to directly measure the biomarkers in the fibroblasts from the skin homogenates.

Lipid accumulation is pronounced in the brain, liver and spleen, organs that are severely affected in this neurovisceral, progressively debilitating and life-threatening disease. However, these tissues are not easily sampled in a clinical trial, even less justified in the paediatric population. Recently, GSL accumulation was also found to be elevated in purified CD19+ B cells (Te Vruchte et al., 2014); but whether these cells are suitable for the diagnostic determination of cholesterol accumulation, remains to be investigated and confirmed. Whether the same observation can be shown in peripheral blood mononuclear cells (PBMCs) remains also to be investigated. For the ganglioside analysis, most publications rely on fibroblast or animal tissue but there are also a couple of publications on CD19+ cells. Upon these reasons it was decided not to rely solely on the PBMC results.

Oxidation products of cholesterol, called Oxysterols, have been shown to be elevated in multiple tissue from NPC mutant mice and in-patient blood samples (Porter et al., 2010). Recently, a large clinical study demonstrated that the oxysterol cholestane-3β,5α,6β-triol can be used as a diagnostic marker for Niemann Pick type C disease (McKay Bounford et al., 2014, Reunert et al., 2016).

Accumulation of sphingoid bases has been seen in NPC patients as well as in mouse models of the disease (Lloyd-Evans and Platt, 2010; Vanier et al., 2015; Lloyd-Evans et al., 2008).

The skin biopsies procedure is minimally invasive and represents a low risk in comparison to other diagnostic procedures that may imply a much higher risk of complications. Other relevant target tissues such as brain, liver and spleen are not easily sampled in a clinical trial, and arguably are not ethically justifiable to sample if punch skin biopsies can be used instead.

In order to perform an exploratory exposure-response analysis, sampling for POP PK will be performed in all patients at Visits 3, 4, 5, and 6 (3, 6, 9 and 12 months respectively). The maximum volume of blood collected for POP PK sampling will be 8 mL in total.

Extensive assay development has been performed to confirm and validate the appropriate procedure/s and to minimise the sampling volumes.

Upon regulations and guidelines, a limited volume of blood will be drawn from each patient during this study (at baseline, 7-14 days post the commencement of multiple dosing, and at the 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60-month visits) that will not exceed the recommended maximum blood sampling volume for children in clinical trials which should not exceed 3% of total blood volume in one draw (Howie, 2011).

7.4. BIOBANK

If the patient or the patient's parent(s)/legal guardian(s) provide consent, the Sponsor will store the excess blood/plasma/serum collected during the study for future research use. The research may include analysis of biomarkers for NPC. This is optional for all patients entering the study and will involve a separate patient consent procedure. Consenting for the storage of excess blood/plasma/serum for future research use by the Sponsor is not a pre-requisite to participating in the study. Samples will be stored for a maximum of 15 years after the last patient has completed the study.

8. OBJECTIVES

8.1. PRIMARY OBJECTIVE

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

8.2. 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 months and every 6 months thereafter until End of Extension Phase at 60 months;
- To evaluate the safety of arimoclomol.

9. INVESTIGATIONAL PLAN

9.1. SUMMARY OF STUDY DESIGN

A prospective, randomised, double-blind, placebo-controlled therapeutic study in patients with confirmed diagnosis of NPC 1 or NPC 2 on or not on miglustat therapy that either 1) have completed Visit 2 (end of study [EOS]) of the CT-ORZY-NPC-001 study or 2) meet the eligibility criteria of this study (CT-ORZY-NPC-001) including a requirement of stable treatment with miglustat for 6 months (if on miglustat therapy) prior to enrolment into CT-ORZY-NPC-002 study. It is anticipated that the majority of patients for inclusion in the CT-ORZY-NPC-002 study would have completed the CT-ORZY-NPC-001 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; each patient's standard of care may, or may not, include miglustat. The study endpoints are documented in Section 9.3.

Patients will be stratified into strata A (on miglustat therapy) and B (not on miglustat therapy). Hereafter, the patients will be randomised to receive placebo or arimoclomol (with an allocation ratio of 1:2).

To confirm the selected dose, patients less than 12 years of age will undergo an arimoclomol single-dose PK evaluation before randomisation and the start of continuous (multiple dosing) treatment.

In order to perform an exploratory exposure-response analysis, sampling for POP PK will be performed in all patients at Visits 3, 4, 5, and 6 (3, 6, 9 and 12 months respectively).

The duration of the blinded phase study period will be 12 months.

Following this, all patients will be offered to continue into the extension phase of the study where every patient will receive arimoclomol and will attend site visits at 18, 24, 30, 36, 42, 48, 54 and 60 months (after patient randomisation). The extension phase runs for 48 months or until arimoclomol has received EU/US 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 or if the study is stopped prematurely (see Section 22.5), the duration of the study will either be extended accordingly (amendment to protocol) or patients may be offered continued treatment with arimoclomol via an early access programme as permitted by local regulation. Early access programmes may vary depending on location and include: compassionate use, named patient, expanded access and managed access programmes.

Continued access to treatment will be contingent on the continued favorable benefit/risk profile of arimoclomol in NPC as assessed by KemPharm Denmark.

Patients will be enrolled in the extension phase only if the investigator deem that the patient is deriving clinical benefits from the trial participation.

Following the review of relevant juvenile toxicology data and PK information from 100% of the patients aged 2 to <12 years, the CT-ORZY-NPC-002 study has now been expanded to include a paediatric substudy in patients aged 6 to <24 months at study enrolment which will assess the safety and tolerability of 36 months of open-label arimoclomol when it is

administered as an add-on therapy to the patient's current prescribed best standard of care; each patient's standard of care may, or may not, include miglustat (refer to APPENDIX V: Paediatric Substudy for description of the substudy). Data from the paediatric substudy will be analysed and reported separately from the data in the main study.

Before undergoing any screening procedures or data collection, patients (and the patients' parent[s]/legal guardian[s]) will be required to sign the Patient Information and Informed Consent Document (PICD) for this study.

Refer to Section 9.4 for the trial timetable/study visits. A schedule for the tests and evaluations to be conducted in this study is found in the flow charts in APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age, APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older and APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients.

The Investigator will contact the patient (or the patient's parent[s]/legal guardian[s]) by telephone (monthly calls during the first 6 months of the blinded phase and every 3-4 months following the start of the extension phase) to 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. Should the patient experience disease progression that is too severe and/or too fast or should there be any safety concerns or should the patient's weight require reassessment in the clinic (in order to confirm if a dose reduction is required), the patient may also attend the site for unscheduled visits.

A Data Safety Monitoring Board (DSMB) will review the safety data (including renal and hepatic data) during the blinded phase of the study.

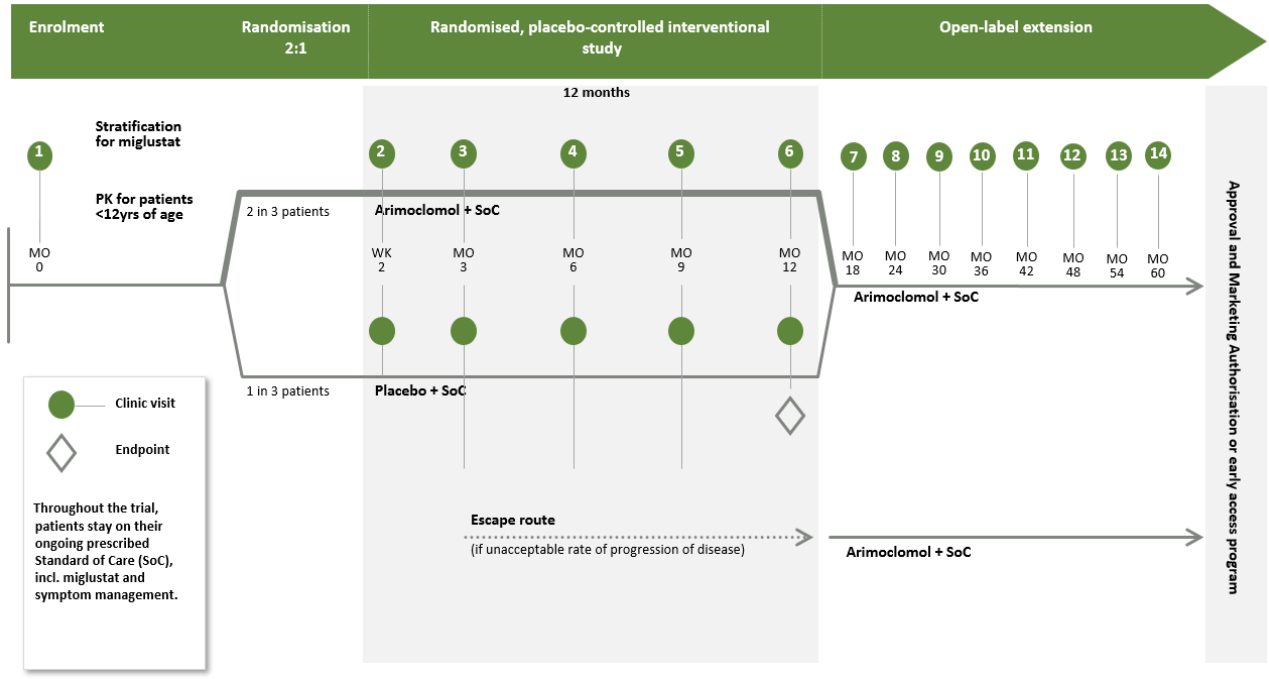
In patients whose disease progression is too severe and/or too fast, the "early escape clause" (refer also to Section 10.5.2) will allow the Investigator to apply the escape route which implies that the patient can be treated with arimoclomol during the blinded phase of the study.

Should a patient discontinue prematurely and choose to withdraw from the study, all effort should be made to have the patient attend the site for a withdrawal visit during the blinded or the extension phase of the study (depending on the time point of withdrawal). Should the patient (or the patient's parent[s]/legal guardian[s]) refuse to attend the withdrawal visit, the date and reason for study discontinuation will be recorded in the electronic case report form (eCRF) as minimum. Refer to Section 10.5.1 for the discontinuation criteria.

Approximately 15-20 sites in 6-9 countries in Europe and US will participate in this study. 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).

The overall study design is summarised in Figure 9-1.

Figure 9-1: Study Design



9.2. DISCUSSION OF TRIAL DESIGN

NPC is a very rare disease in which patients show progressive and significant neurological deterioration. There is no universally accepted marker of the disease. Inter-patient individual disease progression is heterogeneous.

In this Phase II/III study (CT-ORZY-NPC-002), all markers investigated during the initial 12-month placebo-controlled phase of the study will support the therapeutic response evaluation of arimoclomol vs. placebo.

Arimoclomol (or placebo) is given as an add-on therapy to the current best standard of care. Since none of the patients are deprived from their current available therapy it is considered ethically justified to use placebo in this study. In addition to this, the exposure to placebo has been minimised as much as statistically justifiable (i.e. a randomisation scheme of 1:2 [placebo:arimoclomol]) is applied.

The 12-month duration of the blinded study phase is considered to be the minimal duration required in order to be able to identify changes in the disease severity (as assessed by the NPCCSS). In order to monitor the patient's disease progression and the safety of the IMP, as well as to maintain patient motivation, improve patient compliance and minimise patient drop outs, the patient will visit the site every 3 months.

Although the potential benefits of arimoclomol in this patient population still remains to be evaluated, an early escape clause has been implemented in order to ensure that patients experiencing an unacceptable rate of progression, than expected, can receive arimoclomol

(active treatment) during the blinded phase of the study (as per the patient's current protocol schedule). To minimise bias introduced by the families (eager to get active drug), the decision of whether the early escape clause and criteria have been met or not, is to be taken by the investigators and is based upon the NPCCSS score. Also, the frequent visits (every 3 months) are considered to minimise the risk of families requesting unscheduled visits to have the disease severity evaluated, since this could lead to a bias in the estimate of time to "treatment failure".

In general, with regard to the PK characteristics, the age group of 12-18 years (adolescent) is considered to have similar PK as adults, while the lower age groups are less predictable. Therefore the PK profile of arimoclomol is required to be confirmed in patients below the age of 12 before multiple dosing can commence (ref:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf).

In order to perform an exploratory exposure-response analysis, POP PK will be performed in all patients at Visits 3, 4, 5, and 6 (3, 6, 9 and 12 months respectively). The maximum volume of blood collected for POP PK sampling will be 8 mL in total. Sampling times for POP PK were selected based on the anticipated PK profiles in children, robustness to uncertainty in PK and patient convenience.

After the 12-month blinded phase of the study, all patients will receive arimoclomol (active drug). Since the safety profile of arimoclomol in paediatric patients will be well established at this time point, during the extension phase of the study the patients will attend the site for a visit at 18, 24, 30, 36, 42, 48, 54 and 60 months (after patient randomisation). In addition to this, following the start of the extension phase of the study, the site will call the patient every 3-4 months to 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.

Patients will be enrolled in the extension phase only if the investigator deem that the patient is deriving clinical benefits from the trial participation.

Following the review of relevant juvenile toxicology data and PK information from 100% of the patients aged 2 to <12 years, the CT-ORZY-NPC-002 study has now been expanded to include a paediatric substudy in patients aged 6 to <24 months at study enrolment which will assess the safety and tolerability of 36 months of open-label arimoclomol when it is administered as an add-on therapy to the patient's current prescribed best standard of care; each patient's standard of care may, or may not, include miglustat (refer to APPENDIX V: Paediatric Substudy for a description of the substudy). Patients below 2 years of age will be treated with open label arimoclomol and will be analysed and reported separately as compared to the main analysis of the 12 months placebo-controlled study.

9.3. STUDY ENDPOINTS

9.3.1. Primary Endpoint

- 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;

9.3.2. Clinical Status Endpoints

Key Secondary Endpoints:

- Responder analysis of patient's CGI-I score remains stable or shows improvement at 12 months (for the United States Food and Drug Administration [FDA] submission, this endpoint is considered a co-primary endpoint);
- Responder analysis of patient's 5 domain NPCCSS score remains stable or improves at 12 months compared to baseline;
- Time to worsening (as defined by reaching the minimal clinically important difference [MCID] on patient's 5 domain NPCCSS);
- Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 6 and 12 months;
- Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 12 months.

Other Secondary Endpoints:

- Change in 5 domain NPCCSS score at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Responder analysis of the CGI-I score remains stable or shows improvement at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Responder analysis of 5 domain NPCCSS score remains stable or improves at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months compared to baseline;
- Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Changes in each individual domain of the NPCCSS at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Change in the NPC-cdb score (modified "Stampfer Score" [Stampfer et al., 2013]) at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;

- Change in Quality of Life (EQ-5D-Y) at 6, 12 and 18 months and at every 6 months thereafter until End of Extension Phase at 60 months;
- Change in the SARA score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- Change in the 9HPT time at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- CGI-S score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months;
- CGI-I score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

9.3.3. Exploratory Endpoints

- NPC disease progression rate based on the NPCCSS (apart from hearing domains) 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 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

Exploratory subgroup analyses will be performed on the primary and three key secondary endpoints (refer to Sections 9.3.1 and 9.3.2, respectively).

9.3.4. Safety Endpoints

- AEs (disease related and/or treatment/procedure related);
- Haematology;
- Clinical chemistry;
- Vital signs.

9.3.5. Imaging Endpoints

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

9.3.6. Biomarker Endpoints

There are no validated biomarkers in NPC to evaluate disease progression burden and potential therapeutic response. The biomarkers listed (see also Table 18-1) will be explorative to confirm and support clinical observations and characterise the individual patient clinical status at baseline (Visit 1), 6 and 12 months (Yanjanin et al., 2010). Absolute values in the listed biomarkers will be recorded and analysed.

- NPC1 active protein;
- NPC1 protein function (cholesteryl esterification);
- Oxysterol (cholestane-3β,5α,6β-triol);
- Un-esterified cholesterol;
- HSP70;
- GSLs;
- Sphingoid bases;
- Lyso-SM-509.

Changes at 6 and 12 months (placebo versus arimoclomol) will be evaluated.

During the extension phase of the study, the following biomarkers will be analysed:

- Oxysterol (cholestane-3β,5α,6β-triol);
- Un-esterified cholesterol;
- HSP70;
- GSLs;
- Lyso-SM-509.

9.3.7. Other Endpoints

- Patient acceptability/palatability of the IMP (blinded phase study period).

9.4. TRIAL TIMETABLE (STUDY PERIODS)

The trial includes the following visits:

- Visit 1 (Site):
  - Screening;
  - PK to confirm doses for patients less than 12 years of age;
  - Additional PK visits (site) for patients less than 12 years of age if required;
  - Randomisation.
- Blinded Phase:
  - Telephone follow up every month (±7 days) for 6 months after the start of continuous treatment;
  - Visit 2 (site): 7-14 days after the start of continuous treatment;
  - Visit 3 (site): 3 months (±4 weeks) after patient randomisation;
  - Visit 4 (site): 6 months (±4 weeks) after patient randomisation;
  - Visit 5 (site): 9 months (±4 weeks) after patient randomisation;
  - Visit 6 (site)/End of Blinded Phase: 12 months (±4 weeks) after patient randomisation or at patient withdrawal during the blinded phase.

    Visits 2 through 6 will include scoring for disease severity, blood and skin biopsy sampling for biomarkers, as well as assessment of safety, compliance, SARA, 9HPT, CGI-S, CGI-I and Quality of Life.
- Extension Phase:
  - Visit 7 (site): 18 months (±4 weeks) after patient randomisation;
  - Visit 8 (site): 24 months (±8 weeks) after patient randomisation;
  - Visit 9 (site): 30 months (±8 weeks) after patient randomisation;
  - Visit 10 (site): 36 months (±8 weeks) after patient randomisation;
  - Visit 11 (site): 42 months (±8 weeks) after patient randomisation;
  - Visit 12 (site): 48 months (±8 weeks) after patient randomisation;
  - Visit 13 (site): 54 months (±8 weeks) after patient randomisation;
  - Visit 14 (site)/End of Extension Phase: 60 months (±8 weeks) after patient randomisation or at patient withdrawal during the extension phase.

    Visits 7 to 14 will include scoring for disease severity, blood sampling for biomarkers, as well as assessment of safety, compliance, SARA, 9HPT, CGI-S, CGI-I and Quality of Life;
  - Telephone follow up every 3-4 months.

9.5. DATA SAFETY MONITORING COMMITTEE

An independent DSMB consisting of at least 3 external independent members not associated with the conduct of the study or other study committees will on a continuous basis assess the overall safety of the study during the blinded phase of the study. This will include meeting regularly to:

- Review safety data, including the review of renal (e.g. serum creatinine) and hepatic (e.g. aspartate transaminase [AST] and/or alanine transaminase [ALT]) parameters;
- Recommend on the stopping of IMP administration;
- Recommend the premature termination of the study if deemed necessary after a review of the latest available data.

All decisions will be documented in the form of minutes. A DSMB charter will document in more detail the responsibilities, duties and objectives of the individuals and of the committee.

10. SELECTION AND WITHDRAWAL OF PATIENTS

Up to fifty-two (52) patients will be randomised in the study as the final target is to have at least forty (40) evaluable patients (at least 30 of these should be paediatric patients less than 18 years of age). Each patient should:

- Meet **all** of the inclusion and none of the exclusion criteria specified below (refer to Sections 10.2 and 10.3) within the specified time-frame;
- Complete the required activities specified in this protocol;
- Have their data entered on the eCRF.

10.1. INFORMED CONSENT

Each potentially eligible patient (and/or their parent[s]/legal guardian[s]/legally authorised representative [LAR]) will be informed of the study's objectives and overall requirements. Prior to conducting any tests not performed routinely in the treatment of the patient, the Investigator will explain the study fully to the patient and/or his/her parent(s)/legal guardian(s) using the PICD. If the parent/legal guardian is willing for the patient to participate in the study, (s)he will be requested to give written informed consent. The Informed Consent will be signed and personally dated by the parent(s)/legal guardian(s) (according to local laws and regulations) and the Investigator. If capable, the patient should provide assent/consent to participate in the study and also sign and personally date the Informed Consent if possible (according to local laws and regulations). A copy of the signed form(s) will be provided to the parent(s)/legal guardian(s) and the original retained with the source documents. Although nursing staff may be involved in describing the trial to a patient and his/her parent(s)/legal guardian(s), the Investigator must participate in discussions with the patient and/or his/her parent(s)/legal guardian(s) and sign and personally date the Informed Consent.

10.2. INCLUSION CRITERIA

In order to ascertain efficacy, the patient population to be investigated should be as homogeneous as possible in relation to metabolic parameters and clinical and biological disease status.

In order to be eligible for inclusion into this study, each patient must fulfil all of the following inclusion criteria at enrolment (Visit 1):

- **EITHER**

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

  OR

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

  - Diagnosis of NPC1 or NPC2;
  - NPC diagnosis confirmed by:

- Genetically confirmed (deoxyribonucleic acid [DNA] sequence analysis) by mutations in both alleles of NPC1 or NPC2,

OR

- Mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane triol/oxysterols (>2 x upper limit of normal [ULN]).

- Males and females aged from 2 years to 18 years and 11 months;
- Treated or not treated with miglustat;
- If a patient is under prescribed treatment with miglustat, it has to be under stable dose of the medication for at least 6 continuous months prior to inclusion in the CT-ORZY-NPC-002 study;
- If a patient has been discontinued from prescribed treatment with miglustat, they must have been discontinued for at least 3 continuous months prior to inclusion in the CT-ORZY-NPC-002 study;
- Body mass index (BMI) Z-score ≥ -2 standard deviation (SD) for age, according to the World Health Organisation (WHO) standards;
- Presenting at least one neurological symptom of the disease (for example, but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia);
- Ability to walk either independently or with assistance.

- Written informed consent (and assent if appropriate to local laws and regulations) prior to any study-related procedures;
- Willing to participate in all aspects of trial design including blood sampling (PK, blood biomarkers and safety labs), skin biopsies and imaging (ultrasonography of the liver and spleen);
- Ability to travel to the corresponding clinical trial site at the scheduled visit times for evaluation and follow-up;
- All sexually active female patients of child-bearing potential (post-menarchal) must use highly effective contraception during the study and until 3 weeks after the last dose of IMP.

  Highly effective birth control methods include: Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; and vasectomised partner.

  All sexually active male patients with female partners of child-bearing potential (post-menarchal) must use a condom with or without spermicide in addition to the birth control used by their partners during the study and until 3 months after the last dose of IMP.

Sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual intercourse during the study and for 3 weeks after the last dose of IMP (for female patients of child-bearing potential) and for 3 months after the last dose of IMP (for male patients with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Based on recommendations from the Clinical Trial Facilitation Group (CTFG, 2014).

- Ability to comply with the protocol-specified procedures/evaluations and scheduled visits.

10.3. EXCLUSION CRITERIA

Each of the following criteria will be taken as reason for exclusion from participation in the trial:

- Recipient of a liver transplant or planned liver transplantation;
- Severe liver insufficiency (defined as hepatic laboratory parameters, AST and/or ALT greater than three-times the ULN for age and gender (central laboratory assessment);
- Renal insufficiency, with serum creatinine level greater than 1.5 times the ULN (central laboratory assessment);
- Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents);
- In the opinion of the Investigator, the patient's clinical condition does not allow for the required blood collection and/or skin biopsies as per the protocol-specified procedures;
- Treatment with any investigational drug during the study or in the 4 weeks prior to entering the study.

  This includes treatment with any investigational drug during the study in an attempt to treat NPC;
- Pregnancy or breastfeeding;
- Current participation in another trial is not permitted unless it is a non-interventional study and the sole purpose of the trial is for long-term follow up/survival data (registry);
- For patients who have not completed the CT-ORZY-NPC-001 study, fulfilling any of the criteria listed below:
  - Patients with uncontrolled severe epileptic seizures period[a] (at least 3 consecutive severe epileptic seizures that required medication) within 2 months prior to the written consent. This includes patients with ongoing seizures that are not stable in frequency or type or duration over a 2-month period prior to enrolment, requiring change in dose of antiepileptic medication (other than adjustment for weight) over a 2-month period prior to enrolment, or requiring 3 or more antiepileptic medications to control seizures;

[a] An epileptic seizure is a transient symptom of abnormal excessive or synchronous neuronal activity in the brain. The outward effect can be as dramatic as a thrashing movement (tonic-clonic seizure) or as

mild as a brief loss of awareness (absence seizure). It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. Sometimes it is not accompanied by convulsions but a full body slump, where the person simply will lose body control and slump to the ground. Seizures can occur in patients who do not have epilepsy. On the other hand, non-epileptic seizures are paroxysmal events that mimic an epileptic seizure but do not involve abnormal, rhythmic discharges of cortical neurons. These non-epileptic seizures are caused by either physiological or psychological conditions.

- Neurologically asymptomatic patients;
- Severe manifestations of NPC disease that would interfere with the patient's ability to comply with the requirements of this protocol;
- Treatment with any IMP within 4 weeks prior to the study enrolment.

10.4. ASSIGNMENT OF PATIENT NUMBER/ASSIGNING PATIENTS TO TREATMENT GROUPS

At screening, the Investigator will assign a patient number to the patient.

Once the subject is considered by the Investigator to be eligible for the study, the Investigator will create a new patient in the eCRF. Patients will be stratified into strata A (on miglustat therapy) and B (not on miglustat therapy).

Upon randomisation, the eCRF will assign a randomisation number to the patient. The treatment assigned to each patient will be determined according to a computer-generated randomisation list. Patients will be randomised to receive placebo or arimoclomol (with an allocation ratio of 1:2).

10.5. PREMATURE WITHDRAWAL OF PATIENTS FROM STUDY AND REPLACEMENT POLICY

10.5.1. Discontinuation Criteria

Patients (and their parent[s]/legal guardian[s]) will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons. Any withdrawals must be fully documented in the eCRF and should be followed up by the Investigator.

Additionally, the Investigator may withdraw a patient at any time if he/she considers this to be in the patient's best interest.

Patients will be discontinued from the study if at least one of the following criteria has been met:

- Patient's parents/legal guardian have withdrawn informed consent;
- Patient has withdrawn informed assent;
- Safety reasons (decision of the Investigators and/or Sponsor's medical responsible person and/or DSMB);
- Investigator's decision;
- Patient has participated in another interventional clinical trial;

- Patient has received a liver transplantation;
- Patient has died;
- Patient has become pregnant;
- Patient is lost to follow-up. This is defined as when the site is unable to contact the patient (the patient's parents[s]/legal guardians[s]) and it is impossible to obtain any further data;
- Patient meets criteria for IMP administration to be stopped and subsequent withdrawal (refer to Section 11.2.4);
- Patient is un-blinded during the blinded phase of the study due to an emergency (refer to Section 11.4).

If a patient fails to return for a scheduled visit, attempts should be made to contact the patient (or the patient's parent[s]/legal guardian[s]) to ensure that the reason for not returning is not an AE. Likewise, if a patient (and/or the patient's parent[s]/legal guardian[s]) declares his/her wish to discontinue prematurely and withdraw from the study e.g. for personal reasons, an attempt should be made to establish that the true reason is not an AE (bearing in mind the patient is not obliged to state his/her reasons).

Should the patient discontinue prematurely and choose to withdraw from the study, the patient will be asked to attend the site for a withdrawal visit during the blinded or the extension phase of the study (depending on the time point of withdrawal). The visit should take place within 4 weeks of patient withdrawal. The reason for study discontinuation (if known) should be documented in the eCRF, and any AEs followed up until resolution, until the condition stabilizes, until the event is otherwise explained or until the patient is lost to follow up. If the patient is lost to follow up, then this should be noted in the eCRF.

10.5.2. Early Escape Clause and Criteria

The "early escape clause" can be invoked when a set of criteria are met in the event that a participating patient experiences disease progression that is too severe and/or too fast. In such cases, the patient will:

1) Stop receiving the IMP;
2) Be offered treatment with arimoclomol;
3) Continue with their current protocol schedule (see APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age and APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older).

For evaluation of a potential early escape, the three relevant domains of the NPCCSS to be assessed are: Ambulation, Swallowing and Fine Motor Skills.

The investigator will assess the following criteria to determine if the "early-escape clause" is to be invoked for the particular patient:

EITHER

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

OR

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

OR

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

The Investigator will submit all requests for early escape to Worldwide Clinical Trials for review and approval.

10.5.3. Replacement Policy

At least forty (40) patients planned to be evaluable in this study; at least 30 of these should be paediatric patients less than 18 years of age. Up to fifty-two (52) NPC patients will be randomised. No patient drop-outs will be replaced.

An evaluable patient is defined as a patient who:

- Met all of the inclusion and none of the exclusion criteria specified in Sections 10.2 and 10.3 within the specified time-frame,
- Completed Visit 1 and Visit 4 at 6 months, and
- Had his/her eCRF completed.

Should a patient drop out or be withdrawn from the study, their patient study number will not be reallocated. A dropout rate of approximately 23% is estimated to ensure 40 evaluable patients to complete the study. During the study, recruitment may be increased based on an assessment on the number of evaluable patients in the study to date.

11. STUDY MEDICATION

11.1. INVESTIGATIONAL MEDICINAL PRODUCT

11.1.1. Presentation, Storage, Packaging and Labelling of Arimoclomol

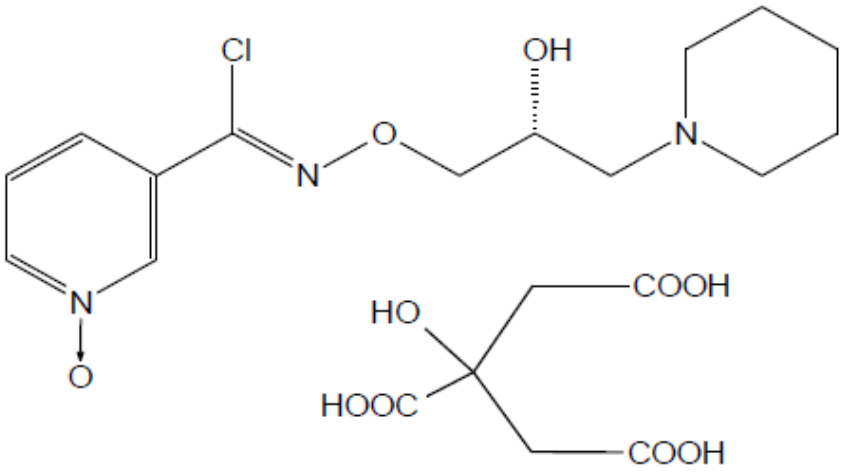
11.1.1.1. Presentation of Arimoclomol

Arimoclomol (N-[(2R)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrate) is a hydroximic acid derivative.

Arimoclomol is a small molecule that up-regulates the HSPs in cells under stress and is a co-inducer of the HSP70 expression. It has been demonstrated in experimental models for NPC that arimoclomol offers the potential to ameliorate signs and symptoms of this severe neurological condition.

Refer to Figure 11-1 for the molecular structure of arimoclomol.

Figure 11-1: Molecular Structure of Arimoclomol



11.1.1.2. Packaging/Labelling of Arimoclomol

Arimoclomol is an odourless, crystalline powder of white or off-white colour supplied in hard capsules of 25 mg, 50 mg, and 100 mg. For each strength, capsule fill will be a powder mix of active pharmaceutical ingredient (API), with the remainder made of [redacted] All strengths will have an identical capsule size (0), and capsule colour (white). Refer also to Table 11-1 for further information.

For the initial PK evaluation (patients less than 12 years of age only), the single-dose of arimoclomol selected for the patient will be presented in a sealed white high-density polyethylene (HDPE) bottle.

For the placebo-controlled part of the study, the capsules (25 mg, 50 mg, and 100 mg) will be supplied in blister packages mounted within wallets which will contain IMP treatment for 7 days. Capsules are blistered into strips of 7 or 6 strips and are in a 42-capsule wallet. A total of 5 wallets will be packaged within a box.

For the extension phase of the study, the capsules (25 mg and/or 50 mg and/or 100 mg) will be supplied in sealed HDPE bottles containing 84 capsules/bottle.

At Visits 1, 3, 4 and 5 the patient will be provided with the required amount of IMP.

At Visit 6 and thereafter in the extension phase of the study, the patient will be dispensed with sufficient arimoclomol to continue treatment.

Each wallet and box, and bottle, will be labelled according to local regulatory requirements.

Table 11-1: Investigational Medicinal Product Description and Packaging

	Blinded Phase	PK Evaluation	Extension Phase
Capsule Type	Hard gelatin capsule, white, size 0	Hard gelatin capsule, white, size 0	Hard HPMC capsule, white, size 0
Packaging material	Blister packages mounted within wallets which contain IMP treatment for 7 days. Capsules are blistered into strips and are in a 42-capules wallet. A total of 5 wallets are packaged within a box.	Capsules are packaged in HDPE bottles with a polypropylene child resistant cap, induction heat sealed with a foil liner at the neck opening.	Capsules are packaged in HDPE bottles with a child resistant cap, induction heat sealed with a foil liner at the neck opening. Bottles contain 84 capsules per bottle.

HPMC: Hydroxypropyl methylcellulose; [redacted]; HDPE: High density polyethylene; IMP: Investigational medicinal product

11.1.1.3. Storage of Arimoclomol

Arimoclomol must be stored in a secure, dry environment at room temperature.

Any deviation from the recommended storage conditions should be immediately reported to the Sponsor.

11.1.2. Presentation, Storage, Packaging and Labelling of Placebo

The placebo capsule is visually indistinguishable from the arimoclomol capsule in size and appearance. The placebo will be presented with an identical weight capsule fill in identical white hard capsules and packaged and labelled as described for arimoclomol (refer to Section 11.1.1.2). The excipient composition, texture, appearance, solubility, smell and flavour of the placebo are carefully matched to mask the identity of the active capsule (arimoclomol).

The storage of the placebo is as described for arimoclomol (refer to Section 11.1.1.3).

11.2. INVESTIGATIONAL MEDICINAL PRODUCT DOSING SCHEDULE AND ROUTE OF ADMINISTRATION

11.2.1. Dose Rationale

A simple allometric scaling method using PK data from Phase I studies to relate size to predicted clearance (CL) (and total exposure), based on total body weight (BW) has been selected as the most appropriate method to adjust dosage in paediatric patients with NPC because:

1. Pharmacokinetics of arimoclomol are linear (proportional) and well characterised in human adults;
2. Bioavailability of arimoclomol in human adults is high;
3. Renal clearance is expected to be a major contributor to overall elimination of arimoclomol and metabolites;
4. Maturation of renal function is considered complete at 2 years of age.

The following equation was applied to predict CL (Mahmood, 2006):

$$\text{CL in the child} = \text{adult CL} \times (\text{weight of the child}/70)^{0.75}$$

Estimated CL values were used to predict exposure (AUC) over a dosing interval at steady state and an appropriate decrease in dose for children based on their total BW. Dose was adjusted based on a target daily exposure limit ($AUC_{0\text{-}24}$) of 12.9 µg.h/mL ensuring a safety factor of 2 compared to daily exposure following repeated dosing at the No Observed Effect Level (NOEL) (400 mg/kg/day) in juvenile rats.

Predicted $AUC_{0\text{-}24}$ values at steady state in the patient population were also compared to observed $AUC_{0\text{-}24}$ at the NOEL in the most sensitive adult toxicological species to ensure a relevant safety margin was maintained.

The final recommendation for dose stratification using a pragmatic choice of weight ranges to ensure a safety ratio of approximately 2 versus NOEL in juvenile rat are presented in Table 11-2. These recommendations are based on a t.i.d dose regime consistent with the dose regime used in adults.

The following numerical assumptions were made for the completion of these predictions:

1. Change in C_{max} and AUC with dose are proportional;
2. Bioavailability of arimoclomol is 100% in children and adults;
3. CL in a healthy 70 kg human adult is 55 L/h - value pooled from available exposure and demographic data in Phase I studies.
4. Protein binding is low (10%) and constant between adults and children.

Table 11-2: Recommended Dose Stratification based on a 2-fold Safety Ratio to Juvenile Rat NOEL (400 mg/kg)

Target safety ratio 2 versus NOEL rat juvenile							
Dose (mg per day)	**Dose (mg) per administration (t.i.d.)**	**Weight range (kg)[a]**	**Minimum predicted $AUC_{(0-8)}$ (µg.h/mL)**	**Maximum predicted $AUC_{(0-8)}$ (µg.h/mL)**	**Maximum predicted AUC_{0-24} (µg.h/mL)[b]**	**Minimum safety ratio versus NOEL rat juvenile 400 mg/kg/day[c]**	**Minimum safety ratio versus NOEL dog 50 mg/kg/day 16 week[d]**
150	50	8-15	2.9	4.6	13.9	1.9	2.9
225	75	>15-22	3.2	4.3	13.0	2.0	3.1
300	100	>22-38	2.9	4.3	13.0	2.0	3.1
450	150	>38-55	3.3	4.3	12.9	2.0	3.1
600	200	>55	3.6	4.4	13.1	2.0	3.1

AUC_{tau}: AUC over the dosing interval at steady state (dosing interval 8 hours).

[a] Calculations assuming maximum weight of 70 kg.

[b] $AUC_{(0-8)}$ X 3.

[c] Based on $AUC_{(0-24)}$ in juvenile rat of 25.7 µg.h/mL.

[d] Based on $AUC_{(0-24)}$ in dog of 40.2 µg.h/mL.

11.2.2. Dose

IMP (arimoclomol and placebo) dosing is based on the patient's BW (refer to Table 11-3):

Table 11-3: Investigational Medicinal Dosing : Based on the Patient Body Weight

Patient Body Weight (BW)	Investigational Medicinal Dosing (IMP) 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 and the IMP dose is to be adjusted as required.

In the event that a patient who is receiving 150 mg IMP per day requires a dose reduction, then a dose of 75 mg per day (25 mg t.i.d) should be administered (refer also to Section 11.2.4).

For individual patients less than 12 years of age, to confirm the corresponding dose, a single dose PK evaluation will be performed by an independent assessor following a single dose of arimoclomol to verify the area under the curve in 0-8 hours (AUC_{0-8}). In the event that patients require a dose reduction (refer also to Section 11.2.4), these patients will be dispensed a further single dose of arimoclomol, and a new single dose PK evaluation will be performed to confirm the corresponding dose. Should further dose adjustments be required, based on the second single dose PK evaluation, the above procedure will be repeated until the correct dose level is found.

Also, in the event that unexpected PK-profiles are obtained (from patients less than 12 years of age) 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. The results of this analysis might lead to dose adjustments as recommended by the independent assessor.

This/these dose reduction(s) will take place prior to randomisation and to commencing continuous dosing of IMP (arimoclomol or placebo, as per the study randomisation).

11.2.3. Dosing Route and Regimen

The IMP (arimoclomol and placebo) may be dispensed only by the Investigator or by a member of staff specifically authorized by the Investigator, as appropriate. The IMP will be dispensed to the patient during site visits or shipped to the patient's house (as appropriate) (refer to Section 13).

Arimoclomol or placebo will be administered orally t.i.d. In the event that IMP administration during the blinded phase study period coincides with the administration of other concomitant medication, the IMP should be administered first.

If required, the IMP can be dispersed in 10-20 mL (i.e. 1-2 tablespoons) of liquid (water, apple juice) or soft foodstuff (yoghurt or apple sauce).

In the dispersed state, the IMP capsules can also be administered via a gastric tube (as applicable). For full administration of the dose, flush the tube with 5 mL of water.

The dispersed product is stable for 8 hours.

11.2.4. Dose Adjustment

Patients less than 12 years of age may have their dose adjusted (decrease) following a single oral dose of arimoclomol based on review of the following criteria by an independent assessor (see also Table 11-4 and Section 11.2.1):

- AUC_{0-8}

In addition, the dose can be adjusted (and subsequent repeated PK assessments performed) (refer to Section 11.2.2), if justified by the independent assessor (e.g. if an unexpected PK-profile is obtained and this could potentially impact the safety of the subject).

In the event that a patient who is receiving 150 mg IMP per day requires a dose reduction, then a dose of 75 mg per day (25 mg t.i.d) should be administered. For this dose group (75 mg per day), the same AUC acceptance limit of 4.6 has to be adhered to (Table 11-4).

Table 11-4: Acceptance Criteria for Pharmacokinetic Evaluation following Single Oral Dose of Arimoclomol (Patients Less than 12 years of Age)

Weight range (kg)[a]	Dose (mg per day)	Dose (mg) per administration (t.i.d.)	Acceptable exposure limit (AUC_{0-8}) to maintain an approx 2-fold safety ratio (µg.h/mL)
8-15	150	50	4.6
>15-22	225	75	4.6
>22-38	300	100	4.6
>38-55	450	150	4.6
>55	600	200	4.6

[a] Calculations assuming maximum weight of 70 kg.

In addition to this, a patient who has commenced continuous dosing with the IMP is to be considered for dose reduction should the following criteria be met:

- Serum creatinine above 1.5 x the patient's baseline creatinine value. Dose adjustment may be temporary however, subsequent dose increase must be discussed with the KemPharm Denmark's medical monitor (or delegate);

  Note: Serum creatinine calculation = Serum creatinine value/baseline serum creatinine value. Result rounded to 1 decimal point as per normal rounding principles.

- Decrease in the patient's weight (as confirmed during a site visit) meeting the lower weight range in the actual dose group (refer to Section 11.2.2 for dosing based on the patients BW).

Upon confirmation of a dose reduction, new IMP kits will be dispensed to the patient at the confirmed lower dose. In the event that this does not coincide with a site visit, the IMP will be shipped to the patient's home.

In order to maintain blinding (refer to Section 11.3) in the event that a dose reduction is due to a patient's elevated serum creatinine values at Visit 2, 2 additional patients (selected at random from across all sites) will also be dispensed new IMP kits but their IMP dose will remain unchanged.

Following confirmation of a dose reduction, the patient should continue their daily dosing at their current IMP dose, until they are in receipt of the new IMP kits, as per Investigator discretion and patient safety.

Administration of IMP will be stopped and the patient withdrawn from the study should the following criteria be met:

- Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 acute kidney injury considered related to the IMP (which corresponds to the serum creatinine increase of above 2-3 x the patient's baseline creatinine value);

  Note: Serum creatinine calculation = Serum creatinine value/baseline serum creatinine value. Result rounded to 1 decimal point as per normal rounding principles.

- CTCAE Grade 3 hepatic related parameters (AST and/or ALT) considered related to the IMP;
- Other CTCAE Grade 3 AEs considered related to the IMP.

The individual patient dose will be adapted if required upon patient's weight changes at every visit (refer to Section 11.2.1 for dosing based on the patients BW).

Refer also to Section 11.3 for the review of the Visit 2 creatinine test results (central lab analysis).

11.2.5. Dose Interruption

If a patient experiences a clinically significant and/or unacceptable toxicity (which is not a discontinuation criterion as listed in Section 10.5.1), dosing may be interrupted and supportive therapy administered as required. All dosing interruptions must be discussed with the KemPharm Denmark's medical monitor (or delegate).

An interruption of up to 4 weeks (calculated from AE start date) is permitted following discussion with the KemPharm Denmark's medical monitor (or delegate) prior to resuming IMP administration at the same dose prior to interruption (unless the criteria are met for dose adjustment as specified in Section 11.2.4).

11.3. BLINDING

To maintain the integrity of the study, access to unblinded information will be restricted throughout until final database lock. The treatment allocation for each patient will be managed via Interactive Response Technology (IRT). Treatment codes will not be made available to anyone who could influence the ongoing treatment and evaluation of patients.

Visit 2 creatinine test results (central lab analysis) will not be sent to the site; instead these results will be reviewed by an independent expert in order to avoid the possible unblinding of the patient. Based upon the available data, any possible effects on the kidneys/creatinine levels will be detectable with 7-14 days (at Visit 2). Any possible changes are expected to be normalized within a period of 3-4 months. Visit 2 creatinine test results will be transferred to Worldwide Clinical Trials Data Management for inclusion in the study database following unblinding of the study data after study completion. The independent expert will contact the investigator in the event that further safety follow up is required.

In the event that a patient requires a dose reduction (refer to Section 11.2.4) at Visit 2, 2 additional patients (selected at random from across all sites) will also be dispensed new IMP kits. Only the patient requiring a dose reduction will receive a lower dose; the IMP dose for the additional 2 patients will remain unchanged.

The DSMB will be provided with unblinded data where appropriate, the DSMB will also have a specified unblinded statistician. Pharmacovigilance department can also request unblinded data as per the requirements for safety reporting.

To ensure blinding, all IMP (placebo, 25 mg, 50 mg, and 100 mg capsules) are identical in size and appearance. In the event the capsules are opened in order to mix or dissolve the contents into liquid or foodstuff, the excipient composition, texture, appearance, solubility, smell and flavour are carefully matched to mask the identity of the capsule fill.

The IMP will be blinded by means of treatment code lists. The IMP packages will also be blinded: The number of capsules per container, and all container parts will be identical and from the same parts batches, the label batches will be the same and the label print will be completed on the same print station, and the position of the label will be applied consistently between treatment groups as well.

11.4. EMERGENCY UNBLINDING

As a double-blind, placebo-controlled study, both the patients and the Investigators are blinded to the IMP assignment.

In addition, all personnel from the CRO and KemPharm Denmark A/S (except for personnel in Product Supply department), laboratory personnel, and others are blinded to the IMP assignment and will remain blinded until the data for the 12-month blinded phase of the study has been validated and locked.

In case of emergency, where knowledge of the blind treatment may influence further care of the patient, the investigator may determine the patient's treatment using IRT. It is strongly encouraged that un-blinding should only take place after consultation with the study Medical Monitor, CRO or KemPharm Denmark A/S, provided that this does not compromise patient safety. If a treatment code is revealed for any reason, the Investigator must notify the CRO immediately and a record will be kept of when it was revealed, by whom and why. If a blind is broken due to an AE or serious adverse event (SAE), a corresponding AE entry must be completed in the eCRF. All SAEs must be reported as documented in Section 15.3.3.7.

In the event of an emergency unblinding, the patient will be withdrawn (refer to Section 10.5).

11.5. INVESTIGATIONAL MEDICINAL PRODUCT STABILITY DURING SHIPMENT

The IMP (arimoclomol and placebo) will be shipped to the centers and to patients' homes at room temperature.

11.6. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

The Investigator (or pharmacist) is responsible for verifying accurate delivery of the IMP and acknowledging receipt of the IMP by signing (or initialling) and dating the documentation provided by or on behalf of Worldwide Clinical Trials and returning it to Worldwide Clinical Trials. A copy will be retained for the Investigator Site File.

The Investigator (or pharmacist) will maintain accountability records that must document all IMP received from the Sponsor, dispensed (as per the doses specified by the protocol/amendment[s]) to the patient, returned by the patient, and returned to the Sponsor (or alternative disposition of unused IMP). In addition to this, the accountability records will document relevant information received by the Investigator (pharmacist) on the IMP shipped directly to the patients' homes. Records should include dates, quantities, batch numbers, expiration dates, and any unique code numbers assigned to the IMP and/or patients.

When IMP is shipped directly to the patient's home, the confirmation of receipt will be documented via the tracking/documentation system of the courier supplying the IMP.

Patients will be required to return all unused IMP (and relevant packaging [used/empty blister packs and used/empty bottles]) 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.

IMP that has been dispensed to a patient and returned unused must not be re-dispensed for a different patient. Unused IMP must not be used for any purpose other than the present study. Patients should be instructed to return unused IMPs, preferably in their original packaging.

The Worldwide Clinical Trials Clinical Research Associate (CRA) will review the drug accountability forms and check all IMP returns prior to making arrangements for their return to the Sponsor or authorising their destruction by the study site.

12. CONCOMITANT THERAPY/MEDICAL MANAGEMENT OF ADVERSE EVENTS

Any medication, which is considered necessary for the patient welfare, may be given at the discretion of the Investigator. Medications/therapies which should be administered as part of the study requirements are listed in Section 12.2.

During the study, patients will remain on their standard prescribed therapy (based on the choice of their treating physician), symptomatic medication (e.g.: corticosteroids, non-steroidal anti-inflammatories, anticonvulsants, tricyclic antidepressants, etc.), vitamins, minerals and food supplements.

There is the potential that arimoclomol could inhibit the elimination of cationic drugs (e.g. cimetidine, ranitidine and trimethoprim) that are significantly eliminated by renal tubular secretion, so concomitant administration of such drugs with the IMP should be done under careful observation.

Medications that are prohibited during the course of this study are listed in Section 12.3.

If a patient experiences a clinical significant and/or unacceptable toxicity, an interruption in IMP dosing can take place as per Section 11.2.5.

Refer to Section 11.2.4 which lists the criteria/toxicities which will result in an IMP dose reduction. Section 11.2.4 also lists the criteria/toxicities which will result in the withdrawal of IMP administration.

12.1. RECORDING OF CONCOMITANT THERAPY

All medications administered during the study and medical procedures (including any unplanned diagnostic, therapeutic or surgical procedures) ongoing at or starting after the time of written consent until the end of the extension phase of the study or patient withdrawal, must be reported in the appropriate section of the case report form (CRF)/eCRF along with dosage information, dates of administration, frequency, route and reasons for use.

12.2. MEDICATIONS THAT MUST BE ADMINISTERED

There is no mandatory therapy in this study. The patients should continue their standard therapy, which should remain unchanged as judged by the treating physician. Any changes to the patient's standard therapy should be recorded in the CRF/eCRF.

12.3. PROHIBITED MEDICATIONS

Any IMP or any product not approved by the European Medicines Agency (EMA) or the FDA.

13. SCHEDULE OF VISITS

Refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age, APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older and APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients.

13.1. SCREENING AND ENROLMENT

The Investigator will carry out the screening and enrolment for each patient; eligibility criteria will be checked for compliance prior to enrolment in the study.

The Investigator will explain the details of the study to the patient (and the patient's parent[s]/legal guardian[s]). The patient (and the patient's parent[s]/legal guardian[s]) will be given a PICD to read for further information about the study (refer to Section 10.1 for more details regarding informed consent).

The Investigator will maintain a Screening Log (as provided by the CRO) for all patients who were screened for the study.

13.1.1. VISIT 1

13.1.1.1. Patients Less than 12 years of Age

Once the patient (the patient's parent[s]/legal guardian[s]) has signed the PICD, the formal screening evaluations and procedures to determine the patient's study eligibility must be completed. Where appropriate, data will be taken from the CT-ORZY-NPC-001 study.

Most patients are anticipated to have completed Visit 2 (EOS) in the CT-ORZY-NPC-001 study.

These evaluations include the following:

- Date of signed informed consent;
- Demographics – date of birth, sex and race;
- Diagnosis:
    - Date of initial symptoms and initial symptom/s description;
    - Date of clinical diagnosis and symptoms/clinical status;
    - Fillipin staining result (if applicable);
    - Cholestane triol/oxysterols (if applicable);
    - Date of confirmed genetic NPC diagnosis;
    - Date and details of the results of the DNA sequence analysis.
- NPC disease history including date of first NPC symptom, history of neurological manifestations and past treatments;
- Medical history (including all concomitant disease[s]);
- Confirmation of study eligibility (inclusion and exclusion criteria);
- SARA (refer to Section 14);

- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Pregnancy test (urine) for post-menarchal female patients;
- Review of concomitant therapy (refer to Section 12);
- Review of AEs that may have occurred since PICD signature (refer to Section 15.3).

The following assessments do not need to be repeated at Visit 1 if these assessments have been performed within 7 days of Visit 1 (e.g. performed at Visit 2 [EOS] for the CT-ORZY-NPC-001 study):

- Physical examination including height (refer to Section 15.2.4 for the list of parameters);
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Electrocardiogram (ECG) (refer to Section 15.2.5);
- Skin punch biopsy for biomarkers analysis (refer to Section 18);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Ultrasound of the spleen and liver (refer to Section 16);
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- Quality of Life scoring (refer to Section 14).

PK evaluation:

- Patients less than 12 years of age will be dispensed and administered a single dose of arimoclomol based on their BW (refer to Section 11.2.1);
- PK sampling for patients less than 12 years of age will be performed at the following time-points:
    - Pre-dose 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 PK results will be reviewed by an independent assessor to confirm the corresponding dose or advise on adjusting the dose of arimoclomol. In the event that the patient requires a dose reduction (refer also to Section 11.2.4), 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.

Patient Randomisation and IMP Dispensing and Administration

- Following confirmation of corresponding dose, the Investigator (or delegate) will randomise the patient;
- The patient will be dispensed enough IMP (arimoclomol or placebo, as per the study randomisation) for treatment. The IMP (arimoclomol or placebo, as per the study randomisation) will be shipped to the patient, who will commence dosing upon receipt of it. Within 1 week following randomisation, the investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone 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.

Results of all the screening evaluations and procedures must be reviewed by the Investigator to ensure that all eligibility criteria have been satisfied prior to patient enrolment. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.1.1.2. Patients 12 years of Age and Older

Once the patient (the patient's parent[s]/legal guardian[s]) has signed the PICD, the formal screening evaluations and procedures to determine the patient's study eligibility must be completed. Where appropriate, data will be taken from the CT-ORZY-NPC-001 study.

Most patients are anticipated to have completed Visit 2 (EOS) in the CT-ORZY-NPC-001 study.

These evaluations include the following:

- Date of signed informed consent;
- Demographics – date of birth, sex and race;
- Diagnosis:
    - Date of initial symptoms and initial symptom/s description;
    - Date of clinical diagnosis and symptoms/clinical status;
    - Fillipin staining result (if applicable);
    - Cholestane triol/oxysterols (if applicable);
    - Date of confirmed genetic NPC diagnosis;
    - Date and details of the results of the DNA sequence analysis
- NPC disease history including date of first NPC symptom, history of neurological manifestations and past treatments;
- Medical history (including all concomitant disease[s]);
- Confirmation of study eligibility (inclusion and exclusion criteria);

- Pregnancy test (urine) for post-menarchal female patients;
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Review of concomitant therapy (refer to Section 12);
- Review of AEs that may have occurred since PICD signature (refer to Section 15.3).

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 height (refer to Section 15.2.4 for the list of parameters);
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- ECG (refer to Section 15.2.5);
- Skin punch biopsy for biomarkers analysis (refer to Section 18);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Ultrasound of the spleen and liver (refer to Section 16);
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- Quality of Life scoring (refer to Section 14);

Patient Randomisation and IMP Dispensing and Administration

- Patient randomisation;
- IMP dispensing and administration: Patients ≥12 years old will be dispensed enough IMP (arimoclomol or placebo, as per the study randomisation) for treatment. Patients will commence continuous dosing with IMP (arimoclomol or placebo) as per the study randomisation upon receipt of the IMP.

  Confirmation of eligibility will be dependent on the availability of the relevant central lab results (refer to Section 10.3). 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. Within 1 week following randomisation, the investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone to confirm that the IMP has been received, the date that the patient has

commenced dosing and whether the patient has experienced any difficulties in taking the IMP.

Results of all the screening evaluations and procedures must be reviewed by the Investigator to ensure that all eligibility criteria have been satisfied prior to patient enrolment. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.2. BLINDED PHASE STUDY PERIOD

13.2.1. Telephone Follow-up (Blinded Phase)

During the first 6 months of the blinded phase of the study, the Investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone every month (±7 days) in order to 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. Telephone follow up will commence 1 month following the commencement of continuous dosing. If required, the Investigator should follow up with the patient more frequently. The Investigator will document the telephone contact and information received in the patient's medical notes and update the relevant sections of the eCRF.

13.2.2. VISIT 2

Visit 2 should take place 7-14 days after the start of continuous treatment with the IMP (arimoclomol or placebo).

The following procedures should be performed:

- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
  - Haematology (refer to Section 15.2.2 for the list of parameters);
  - Clinical chemistry (refer to Section 15.2.3 for the list of parameters).
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP (arimoclomol or placebo) administration;
- Patient acceptability/palatability of the IMP (refer to Section 19).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.2.3. VISIT 3

Visit 3 should take place at the site 3 months (±4 weeks) after patient randomisation.

The following procedures should be performed:

- Patient weight;

- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters).
- NPCCSS (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP dispensing: Patients will be dispensed enough IMP (arimoclomol or placebo) for treatment;
- IMP (arimoclomol or placebo) administration;
- Blood sample for POP PK (refer to Section 17.2.2);
- Patient acceptability/palatability of the IMP (refer to Section 19).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.2.4. VISIT 4

Visit 4 should take place at the site 6 months (±4 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- ECG (refer to Section 15.2.5);
- Skin punch biopsy for biomarkers analysis (refer to Section 18);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Ultrasound of the spleen and liver (refer to Section 16);
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);

- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- 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;
- IMP dispensing: Patients will be dispensed enough IMP (arimoclomol or placebo) for treatment;
- IMP (arimoclomol or placebo) administration;
- Blood samples for POP PK (refer to Section 17.2.2);
- Patient acceptability/palatability of the IMP (refer to Section 19).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.2.5. VISIT 5

Visit 5 should take place at the site 9 months (±4 weeks) after patient randomisation.

The following procedures should be performed:

- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- NPCCSS (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP dispensing: Patients will be dispensed enough IMP (arimoclomol or placebo) for treatment;
- IMP (arimoclomol or placebo) administration;
- Blood sample for POP PK (refer to Section 17.2.2).

13.2.6. VISIT 6 (End of Blinded Phase/Withdrawal during Blinded Phase)

Visit 6 should take place at the site 12 months (±4 weeks) after patient randomisation or within 4 weeks of patient withdrawal during the blinded phase of the study.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- ECG (refer to Section 15.2.5);
- Skin punch biopsy for biomarkers analysis (refer to Section 18);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- Ultrasound of the spleen and liver (refer to Section 16);
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- 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;
- Dispensing of sufficient arimoclomol to continue treatment (for patients who have not withdrawn from the study);
- Arimoclomol administration (for patients who have not withdrawn from the study);
- Blood samples for POP PK (refer to Section 17.2.2);
- Patient acceptability/palatability of the IMP (refer to Section 19).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.3. EXTENSION PHASE

13.3.1. Arimoclomol Dispensing

Following Visit 6 (end of the blinded phase of the study), patients will be dispensed with 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.

13.3.2. Telephone Follow-up (Extension Phase)

Following the start of the extension phase of the study, the Investigator will contact the patient (or patient's parent[s]/legal guardian[s]) by telephone every 3-4 months in order to 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. If required, the Investigator should follow up with the patient more frequently. The Investigator will document the telephone contact and information received in the patient's medical notes and update the relevant sections of the eCRF.

13.3.3. VISIT 7

Visit 7 should take place at the site 18 months (±4 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);

- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.3.4. VISIT 8

Visit 8 should take place at the site 24 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
  - Haematology (refer to Section 15.2.2 for the list of parameters);
  - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
  - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;

- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration;
- Blood samples for POP PK (refer to Section 17.2.2).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.3.5. VISIT 9

Visit 9 should take place at the site 30 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.3.6. VISIT 10

Visit 10 should take place at the site 36 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

13.3.7. VISIT 11

Visit 11 should take place at the site 42 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;

- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

13.3.8. VISIT 12

Visit 12 should take place at the site 48 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);

- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

13.3.9. VISIT 13

Visit 13 should take place at the site 54 months (±8 weeks) after patient randomisation.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
    - Haematology (refer to Section 15.2.2 for the list of parameters);
    - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
    - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;

- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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;
- Dispensing of sufficient arimoclomol to continue treatment;
- Arimoclomol administration.

13.3.10. VISIT 14 (End of Extension Phase/Withdrawal during Extension Phase)

Visit 14 should take place at the site 60 months (±8 weeks) after patient randomisation or within 4 weeks of patient withdrawal during the extension phase of the study.

The following procedures should be performed:

- Physical examination (refer to Section 15.2.4 for the list of parameters);
- Patient weight;
- Vital signs (refer to Section 15.2.4 for the list of parameters);
- Blood sample for:
  - Haematology (refer to Section 15.2.2 for the list of parameters);
  - Clinical chemistry (refer to Section 15.2.3 for the list of parameters);
  - Biomarkers analysis (refer to Section 18).
- Pregnancy test (urine) for post-menarchal female patients;
- NPCCSS (refer to Section 14);
- NPC-cdb score (refer to Section 14);
- SARA (refer to Section 14);
- 9HPT (refer to Section 14);
- CGI-S and CGI-I (refer to Section 14);
- Quality of Life scoring (refer to Section 14);
- Review of concomitant therapy;
- Review of AEs that may have occurred following the PICD signature;
- IMP return: Patients will be required to return all unused IMP (and relevant packaging [used/empty bottles]) 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.

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.4. UNSCHEDULED VISIT

The patient can return to the site for an unscheduled visit should the patient experience an unacceptable rate of progression or should there be any safety concerns or should the patient's weight require reassessment in the clinic (in order to confirm if a dose reduction is required).

The following procedures should be performed:

- Blood sample for:
  - Haematology (refer to Section 15.2.2 for the list of parameters);
  - Clinical chemistry (refer to Section 15.2.3 for the list of parameters).
- NPCCSS (refer to Section 14);
- Concomitant therapy;
- AEs that may have occurred following the PICD signature;
- IMP (arimoclomol or placebo) 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
  - IMP dispensing:
    - Blinded phase: Patients will be dispensed enough IMP for treatment.
    - Extension phase: Patients will be dispensed sufficient arimoclomol to continue treatment.
  - Patients will be required to return all unused IMP (and relevant packaging [used/empty blister packs or used/empty bottles]) 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.
- IMP (arimoclomol or placebo) administration (depending on the study phase – blinded phase or extension phase);
- Blood samples for POP PK *at the discretion of the Investigator* (refer to Section 17.2.2).

Should any of the blood samples collected for the purposes of the study be compromised or destroyed in error, a repeat sample should be taken during the visit. Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in the PICD.

13.5. WITHDRAWAL/PREMATURE STUDY DISCONTINUATION

Should the patient discontinue prematurely and choose to withdraw from the study, the patient will be asked to attend the site for the relevant visit: Withdrawal during the blinded phase of the study (refer to Section 13.2.6) or withdrawal during the extension phase of the study (refer to Section 13.3.6).

The Investigator should document the reason for study discontinuation in the eCRF.

In the case of an ongoing AE, appropriate safety evaluations should be repeated more frequently and/or additional tests performed at any time when clinically indicated or at the discretion of the Investigator. All ongoing AEs and SAEs will be followed up until resolution,

until the condition stabilizes, until the event is otherwise explained or until the patient is lost to follow up. If the patient is lost to follow up, then this should be noted in the eCRF.

14. ASSESSMENTS OF CLINICAL STATUS

14.1. SPECIFICATION OF CLINICAL STATUS PARAMETERS

The following will be assessed:

- NPC Disease Severity Scores;
- SARA;
- 9HPT;
- CGI-S;
- CGI-I;
- Quality of Life scoring.

14.2. METHODS AND TIMING

Refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age, APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older and APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients for the respective Study Flow Charts documenting the timing of the relevant assessments.

14.2.1. Niemann-Pick Disease Type C Disease Severity Scores

The NPC disease severity and disease status scores (NPCCSS, NPC-cdb score [refer to Table 14-1]) will be completed. The NPCCSS template and NPC cdb template will be provided for use in this study.

Table 14-1: Niemann-Pick Disease Type C Disease Severity Scoring Models

Disease Severity Scoring Model	Reference
NPC clinical severity scale (NPCCSS)	Yanjanin et al., 2010 – NPCCSS scoring sheet version 1.0 dated 01 April 2016 is used for CT-ORZY-NPC-002 study.
NPC-cdb score (V1.0 dated 01 February 2013)	Stampfer et al., 2013 – modified version used for CT-ORZY-NPC-002 study.

NPC-cdb: Niemann-Pick type C Clinical Database.

14.2.2. Scale for Assessment and Rating of Ataxia

The SARA will be completed as per http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=1242.

14.2.3. Nine-hole Peg Test

The 9HPT will be completed as per http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=925.

14.2.4. Clinical Global Impression Scale – Severity and Clinical Global Impression Scale – Improvement

The CGI-S and CGI-I will be completed as per Guy, 1976 which has been modified to exclude "not assessed".

14.2.5. Quality of Life

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

15. ASSESSMENTS OF SAFETY

15.1. SPECIFICATION OF SAFETY PARAMETERS

The following safety parameters will be assessed:

- AEs;
- Haematology and clinical chemistry;
- Physical examination and vital signs;
- ECG.

AEs will be recorded from the time of consent until to the end of the extension phase of the study (main study), end of the study (paediatric substudy) or patient withdrawal.

Laboratory parameters will be recorded during the Blinded Phase study period at baseline (Visit 1), 7-14 days after the commencement of continuous dosing, at 3, 6 and 12 months (placebo versus arimoclomol), during the Extension Phase at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

Vital signs will be recorded during the Blinded Phase study period at baseline (Visit 1), 7-14 days after the commencement of continuous dosing, at 3, 6, 9, and 12 months (placebo versus arimoclomol), during the Extension Phase at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

Physical examination and ECG will be recorded during the Blinded Phase study period at baseline (Visit 1), 6 and 12 months (placebo versus arimoclomol). Physical examination will also be performed during the Extension Phase at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.

15.2. METHODS AND TIMING

Refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age, APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older and APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients for the respective Study Flow Charts documenting the timing of the relevant assessments.

15.2.1. Adverse Events

AEs (disease related and/or treatment related) reported by the patients (and/or their parent[s]/legal guardian[s]) or noticed by the site staff will be recorded in the eCRF (refer to Section 15.3 for more information). The site will also perform telephone follow up with the patient (or patient's parent[s]/legal guardian[s]) to follow up on the status of the patient and whether the patient has experienced any new AEs or the worsening of any existing AEs (refer to Sections 13.2.1 and 13.3.2 for more detail).

15.2.2. Haematology

Haematology samples will be sent to a central laboratory for analysis. Details of the central laboratory, related procedures and assays are described in the Central Laboratory Manual.

The following haematology tests will be performed:

- 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 percentage of WBC).

15.2.3. Clinical Chemistry

Clinical chemistry samples will be sent to a central laboratory for analysis. Details of the central laboratory, related procedures and assays are described in the Central Laboratory Manual.

The following serum clinical chemistry tests will be performed:

- Sodium;
- Potassium;
- Chloride;
- Magnesium;
- Iron;
- Calcium;
- Phosphate;
- Creatinine (serum) (refer also to Section 11.3 for the review of Visit 2 results);
- Blood urea nitrogen;
- Triglycerides;
- High-density lipoprotein (HDL)/low-density lipoprotein (LDL);
- Cholesterol;
- ALT;
- AST;
- Total bilirubin;
- Gamma-glutamyltransferase (GGT);
- Alkaline phosphatase (AP);
- Lactate dehydrogenase (LDH);
- Albumin.

15.2.4. Physical Examination and Vital Signs

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.

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

New or worsening clinically significant abnormalities will be reported as an AE.

15.2.5. Electrocardiogram

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. The ECG report must be reviewed by the Investigator and any clinically relevant findings should be reported in the eCRF. Any new or worsening clinically significant abnormalities will be followed up with the patient and reported as an AE.

15.3. ADVERSE EVENT REPORTING

It is the Investigator's responsibility to ensure compliance with reporting of AEs from his/her site.

Safety data will be collected from the time of written informed consent and ends at the end of the extension phase of the study (main study), end of the study (paediatric substudy) or patient withdrawal. All ongoing AEs and SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained or until the patient is lost to follow up.

Any AE (including an AE that leads to death) that occurs after the end of the extension phase of the study (main study) or end of the study (paediatric substudy), which the Investigator assesses as related to a study procedure and/or medicinal product, should also be reported as an AE or SAE.

All AEs should be followed until they are resolved or a clinically-stable endpoint is reached if they are considered chronic.

15.3.1. Definition of an Adverse Event

An Adverse Event (AE) is defined as: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can also refer to an untoward response to the administration of the IMP, but can also occur as a result of the protocol-required procedures or be unrelated to both and include worsening of pre-existing conditions, for example.

AEs include the following:

- Suspected adverse medication reactions;
- Reactions from medication overdose, abuse, sensitivity, or toxicity;

- Apparently unrelated illnesses, including the worsening of a pre-existing illness;
- Injury or accidents;

  Note: If a documented medical condition is known to have caused the injury or accident, only the accident should be reported as an AE;

- New or aggravated clinically relevant abnormal medical finding at a physical examination as compared with previous assessments;
- Laboratory abnormalities or other abnormal assessments (e.g. physical examination, vital signs, ECG) that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.

15.3.2. Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;

  Note: Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease under investigation.

  All deaths occurring on the study or up to an including the end of the extension phase of the study or patient withdrawal must be reported.

- Is life-threatening;

  A life-threatening event places the patient at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient hospitalization or prolongation of existing hospitalization;

  Note: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether other events meet the serious criteria, the event is to be considered serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity;

  Note: The term "significant disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, hospital, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect;
- Is an important medical event(s) that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in

an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in such instances.

15.3.3. Recording and Reporting of Adverse Events

All AEs and SAEs, as defined above, encountered during the clinical study will be reported in the appropriate section of the CRF/eCRF. Information will include the following:

- Duration of the AE (onset/resolution dates);
- Relationship to the IMP (refer to Section 15.3.3.6);
- Severity (refer to Section 15.3.3.5);
- Concomitant therapy given (or other action taken);
- Action taken with respect to the IMP.

If an AE increases in severity it will be recorded as a new record with the same AE identifier.

AE data should be obtained through observation of the patient, from any information volunteered by the patient (and the patient's parent[s]/legal guardian[s]) and through patient (and the patient's parent[s]/legal guardian[s]) questioning. The patient may be asked "Do you have any health problems?" or "Have you had any health problems since your last site visit?"

15.3.3.1. Reporting of Signs and Symptoms versus a Diagnosis

Recording a diagnosis (when possible) is preferred to record a list of associated signs and symptoms. However, if a diagnosis is known but there are associated signs or symptoms not generally attributed to the diagnosis, the diagnosis and each sign or symptom must be recorded separately.

15.3.3.2. Disease Progression

Disease progression can be considered as a worsening of a patient's condition that is being studied. It may be reflected by an increase in the severity of the condition or an increase in the symptoms. Disease progression during the blinded phase of the study may result in the patient meeting the early escape clause and criteria (refer to Section 10.5.2). Disease progression and any events that are unequivocally due to disease progression should be recorded only in the CRF/eCRF and should not be reported as an AE.

15.3.3.3. Death

All deaths that occur during the AE Reporting period (refer to Section 15.3.4) must be reported as follows:

- Death due (or clearly due to) to disease progression should be documented in the CRF/eCRF but should not be reported as an SAE;
- Death that is not due (or not clearly due) to disease progression should be documented in the CRF/eCRF and as a SAE within 24 hours of the investigator's knowledge of the event (refer to Section 15.3.3.7).

15.3.3.4. Pregnancy

Should a pregnancy occur in a female patient or the partner of a male patient, it must be reported in accordance with the procedures described in Section 15.3.3.7. Pregnancy in itself is not regarded as an AE.

Female patients who become pregnant during the study should be withdrawn (refer to Section 10.5.1).

15.3.3.5. Definition of Severity of Adverse Events

Severity of any AE will be graded according to National Cancer Institute (NCI) CTCAE Version 4.03 (14 June 2010), where applicable.

If an AE occurs that is not listed in the CTCAE, the Investigator will evaluate its severity using the definitions in Table 15-1.

Table 15-1: Definition of Severity of Adverse Events

Mild	**Grade 1** – Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	**Grade 2** – Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	**Grade 3** – Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])
Life Threatening	**Grade 4** – Results in risk of death, organ damage, or permanent disability (unacceptable)
Death	**Grade 5** – Event has a fatal outcome

Note: **Severe** is a measure of intensity whereas an event must meet one of the criteria for serious events listed in Section 15.3.2 to be considered **serious**; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 15.3.2. An AE that is assessed as Grade 3 (severe) or Grade 4 (potentially life-threatening) should not be confused with a SAE.

15.3.3.6. Definition of Relationship of AEs to a Medicinal Product and/or Study Procedure

The Investigator must assess the possible relationship between the AE and the IMP and/or study procedure and/or the patient's underlying condition and record that assessment in the CRF/eCRF. The Investigators is to make his/her own assessment of each SAE to be recorded on the CRF/eCRF and on the SAE form.

The Investigator should provide a Yes or No assessment as to whether there is a reasonable possibility that the event may have been caused by the IMP and/or study procedure.

KemPharm Denmark A/S will evaluate all SAEs with respect to seriousness, causality and expectedness. The expectedness of an SAE considered to be related to the IMP will be determined according to the IB.

The relationship should be assessed according to the criteria below:

Definitely Related	AEs that are temporally linked and for which the study product is the most likely explanation, which disappear or decrease when not using study product and reappear when using study product
Probably Related	AEs that are temporally linked and for which the study product is more likely to be the explanation than other causes, which may improve when not using study product
Possibly Related	AEs that could equally well be explained by study product or other causes, which are usually temporally linked and may improve when not using study product but do not reappear when using study product
Unlikely Related	AEs that may be temporally linked, but which are much more likely to be due to other causes than study product and which do not get worse with continuing use of product
Not Related	AEs that can be clearly explained by extraneous causes and for which there is no plausible association with study product, or AEs for which there is no temporal relationship

15.3.3.7. SAE Reporting Procedure for Investigators

The Investigator must report (by fax, telephone or email) all initial and follow-up SAE reports to the safety vendor within 24 hours of awareness of an SAE. Please refer to the SAE Reporting Contact Details document.

If, for any reason, it is not possible to complete all sections of the SAE form within 24 hours, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE form. In addition, the event must be documented in the CRF/eCRF.

Information on SAEs will be recorded on a SAE form. Blank copies are included in the study Investigator's File.

This report should contain as much information as possible and must include an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

Photocopies of the subject's medical records should not be sent in lieu of completion of the SAE Form. Medical records, laboratory reports etc. should only be sent to the Safety vendor upon request. Importantly, when subject records are shared outside the site, all subject identifiers, with the exception of the subject number, shall be redacted on the copies of the medical records before submission.

15.3.3.8. Follow-up SAE Reports

For all SAEs where important or relevant information is missing, active follow-up should be undertaken. Investigators or other site personnel should inform the safety vendor of any follow-up information on a previously reported SAE immediately but no later than 24 hours after they become aware of the SAE. The follow-up information must be presented on an SAE form marked as follow-up. It is necessary only to provide the new information, with the SAE form signed by an Investigator.

The Investigator will ensure that all the necessary information is provided within the timelines stipulated by safety vendor when the request for information is made.

Follow-up reports (as many as required) should be completed and faxed following the same procedure above.

15.3.3.9. Reporting Serious Adverse Events to the Independent Ethics Committee/ Institutional Review Board

The Investigator is responsible for informing local Independent Ethics Committees (IECs)/ Institutional Review Board (IRBs) of the applicable safety reports in compliance with local regulations. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigator's Files and provided to Worldwide Clinical Trials.

The Sponsor, or its designees, Worldwide Clinical Trials or safety vendor, will inform Investigators, central IECs/IRBs and regulatory authorities of applicable safety reports, as required.

15.3.3.10. Reporting of Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE, the nature or severity of which is not consistent with the reference safety information (RSI) of the study drug in the IB and for which there is at least a reasonable possibility of a causal relationship with the study drug.

The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the concerned authorities, central IECs/IRBs and Investigators, and in any case no later than seven days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs shall be reported to the concerned authorities, central IES/IRBs and Investigators as soon as possible but within a maximum of fifteen days of first knowledge by the Sponsor. The Sponsor will report all SUSARs via the EudraVigilance Clinical Trials (CT) Module or Council for International Organizations of Medical Sciences (CIOMS) forms.

The Investigator is responsible for informing local IECs/IRBs of the applicable safety reports in compliance with local regulations. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigator's Files and provided to Worldwide Clinical Trials for filing.

15.3.4. Adverse Event Reporting Period

ALL AEs that occur from the time of written informed consent to the end of the extension phase of the study (main study), end of the study (paediatric substudy) or patient withdrawal, will be recorded in the CRF/eCRF. All ongoing AEs and SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained or until the patient is lost to follow up.

All new AEs or the worsening of any ongoing events from the time of informed consent will be recorded on the AE pages of the CRF/eCRF.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

Any untoward event that occurs after the AE reporting period but which the Investigator assesses as possibly related to the IMP or a study procedure should also be reported as an AE or SAE.

16. ASSESSMENTS OF IMAGING

16.1. SPECIFICATION OF IMAGING PARAMETERS

The following will be performed:

- Ultrasound (liver and spleen).

16.2. METHODS AND TIMING

An ultrasound will be performed in order to document changes in the size of the liver and spleen and any clinical relevant findings.

Refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age and APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older for the respective Study Flow Charts documenting the timing of the relevant assessment.

17. ASSESSMENTS OF PHARMACOKINETICS

17.1. SPECIFICATION OF PHARMACOKINETIC PARAMETERS

The following PK parameters will be assessed only for patients less than 12 years of age:

- AUC_{0-8};
- $C_{max;}$
- Additional assessments of arimoclomol concentration can be performed in the event of unexpected PK-profiles (refer to Section 11.2.1).

For POP PK of arimoclomol and metabolites (if relevant) assessed for ALL patients:

- PK data collected at all visits will be incorporated into a POP PK model.

17.2. METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING PHARMACOKINETIC PARAMETERS

17.2.1. Patients less than 12 years of Age: Pharmacokinetic Profiling to confirm Dose Selection

The PK samples will be collected through venipuncture and the sampling time points are as follows:

- 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 same watch/clock should be used for all time measurements.

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 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.

Further instruction on PK sampling are described in a separate Central Laboratory Manual.

The volume of blood taken per venipuncture sample is no more than 1 mL.

Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in Section 7.3 and in the PICD.

17.2.2. Population Pharmacokinetic Samples: All Patients aged >2 Years

The POP PK samples will be collected through venipuncture and the sampling time points are as follows:

- Visits 3 and 5: 3 hours (±1 hour) following dosing;
- Visits 4, 6, and 8: 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;

The same watch/clock should be used for all time measurements.

The following information should be noted down:

1. The precise time of the administration of the last 2 IMP doses prior to POP PK sampling;
2. The precise time of the blood sampling;
3. The selected route for the IMP administration including any type of liquid/soft foodstuff used for the administration (as applicable).

Further instruction on PK sampling are described in a separate Central Laboratory Manual.

The volume of blood taken per venipuncture sample is no more than 1 mL.

Care should be taken to ensure that the maximum amount of blood drawn does not exceed what is stated in Section 7.3 and in the PICD.

18. ASSESSMENTS OF BIOMARKERS

18.1. SPECIFICATION OF BIOMARKER PARAMETERS

The biomarker parameters (as listed in Table 18-1) will be assessed.

Table 18-1: Niemann-Pick Disease Type C Biomarkers

NPC Biomarkers	Sample	
	Blood Sample	Skin Punch Biopsy
NPC1 active protein	X	X
NPC1 protein function: Cholesteryl esterification	X	
Oxysterol (cholestane-3β,5α,6β-triol)	X	
Un-esterified cholesterol	X	X
HSP70	X	
Glycosphingolipids	X	
Sphingoid bases	X	
Lyso-SM-509	X	

18.2. METHODS AND TIMING

Biological markers related to the NPC disease progression will be assessed in blood and skin punch biopsy samples. Samples will be sent to the designated central laboratory for analysis. Details of the central laboratory, related procedures and assays are described in a separate Central Laboratory Manual.

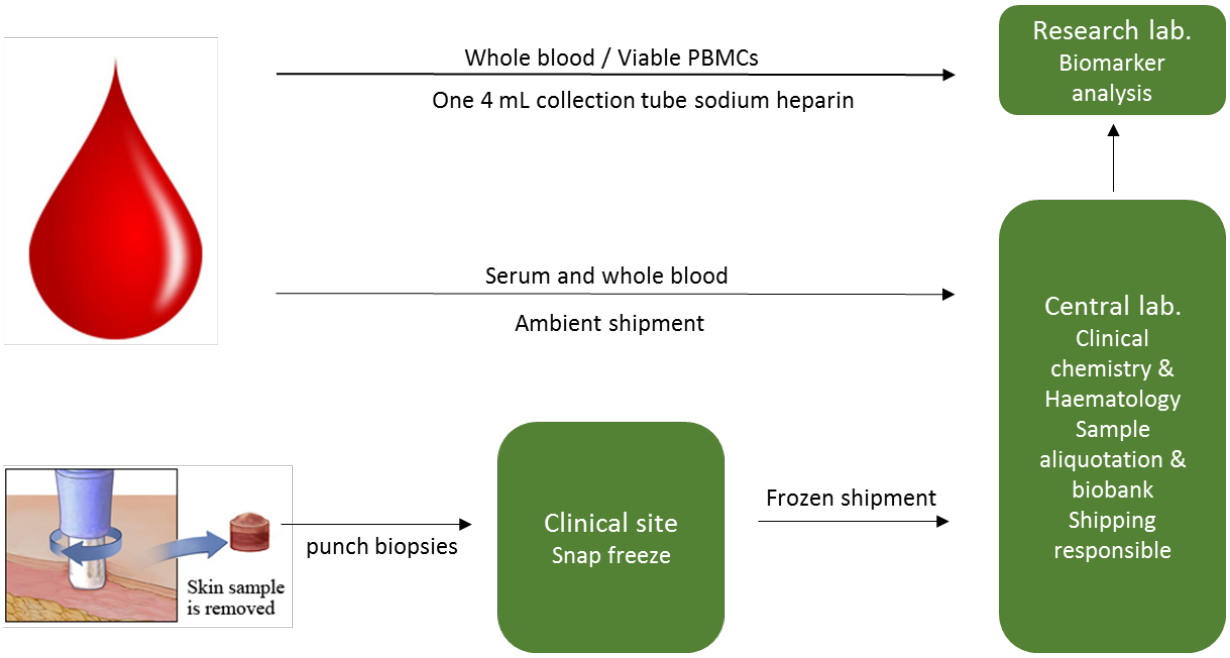
All biomarkers will be assessed during the blinded phase of the study (refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age and APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older for the respective Study Flow Charts documenting the timing of the relevant assessments). During the extension phase of the study, the following biomarkers will be analysed (refer to APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients for the Study Flow Chart documenting the timing of the relevant assessments):

a. Oxysterol (cholestane-3β,5α,6β-triol);
b. Un-esterified cholesterol;
c. HSP70;
d. GSLs;

e. Lyso-SM-509.

The sampling procedure is summarised in Figure 18-1.

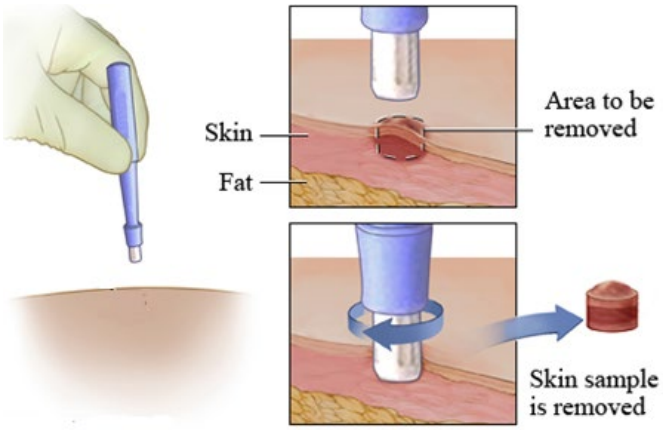
Figure 18-1: Biomarker Sampling Procedure



18.2.1. Skin Punch Biopsy

A punch skin biopsy is a short procedure (1-2 minutes) to remove a small piece of skin tissue. Skin punch biopsies are usually done while the child is fully awake, although the area of skin where the biopsy is taken will be numbed. The punch skin biopsy instrument is gently inserted into your child's skin, rotated and a small circle of skin is carefully removed (refer to Figure 18-2).

Figure 18-2: Skin Punch Biopsy Procedure



The skin punch biopsy is defined as “minimal risk” procedure in children participating in clinical research which represents an opportunity to understand, prevent, or alleviate a serious problem.

19. ASSESSMENTS OF OTHER ENDPOINTS

19.1. SPECIFICATION OF OTHER PARAMETERS

- Treatment failures;
- Change in use of NPC medication;
- Patient acceptability/palatability of the IMP.

19.2. METHODS AND TIMING

The difference in number of treatment failures (defined as patients meeting early escape clause and criteria) at 12 months will be assessed.

The change in use of NPC medication (including miglustat therapy) will be assessed at 12 months and at 18 months and at every 6 months thereafter until End of Extension Phase at 60 months.

The patient's acceptability/palatability of the IMP will be assessed during the blinded phase study period using the hedonic scale at 7-14 days after the commencement of continuous dosing, 3, 6 and 12 months. The hedonic scale is a validated scale developed to test palatability of food (Chen et al., 1996) and has been extensively used to assess palatability of flavoured medications (Matsui, 2007). The patient (the patient's parents[s]/legal guardians[s]) will be asked to use the hedonic scale to rate the palatability of the IMP based on the patient's reaction to the IMP.

Telephone follow up (monthly calls during the first 6 months of the blinded phase and every 3-4 months following the start of the extension phase) will include assessment of whether the patient has experienced any difficulties in taking the IMP.

Refer to APPENDIX II: Study Flow Chart: Blinded Phase Study Period: Patients less than 12 years of age, APPENDIX III: Study Flow Chart: Blinded Phase Study Period: Patients 12 Years of Age and Older and APPENDIX IV: Study Flow Chart: Extension Phase: ALL Patients for the respective Study Flow Charts documenting the timing of the relevant assessments.

20. EVALUATION OF RESULTS

20.1. SAMPLE SIZE AND STUDY POWER

No formal statistical calculation of sample size has been used.

However, the following has been considered to try to ensure that a suitable number of patients will be recruited. In the ASIS study (Protocol Number ASIS-001: A retrospective, non-interventional study of the data of patients diagnosed with NPC in order to confirm ASIS as a disease progression predictive model/tool) (15 patients) the mean rate of progression was 3.6 points per year and the SD was 2.2. Assuming this SD, a study with 30 patients randomised to arimoclomol and 15 patients randomised to placebo has 80% power to detect a difference between arimoclomol and placebo of approximately 2 units on the NPCCSS at the 5% significance level. This would be based on a simple two-sample *t*-test. Use of covariates and a repeated measurements model is expected to improve the power/allow a smaller difference to be detected.

20.2. STATISTICAL METHODS

Statistical analyses will be performed by Larix A/S. Statistical analyses will be carried out using SAS®, Version 9.3 or later, SAS Institute, Cary, Northern Carolina, United States of America (USA).

The statistical methods summarised below, for the 12-month blinded phase study period and the extension phase of the study, will be described in detailed statistical analysis plan(s) (SAP[s]) which will be finalized prior to relevant database's lock. Any deviations from the planned analysis as described in the SAP(s) will be justified and recorded in the final clinical study report.

20.2.1. General Considerations

Descriptive analyses will be performed. Data will be summarised as follows: Continuous variables by descriptive statistics (number of patients [N], mean, SD, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %).

Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed for reporting summary statistics.

Baseline is defined as the latest assessment prior to randomisation. If a baseline value is missing, no change from baseline will be calculated.

20.2.2. Other Considerations

For MCID, the CGI-S and CGI-I will be used as an anchor to estimate a threshold for determining the point at which change on the NPCCSS is considered meaningful. For both clinician assessments a 1-categorical change (reduction in severity by 1-category and improvement by 1-category respectively) between baseline and end of treatment will be used to provide an estimate on each anchor.

20.2.3. Populations for Analysis

Summaries will be presented for all patients who were entered into the study and assigned a patient study number.

The Full Analysis Set (FAS) will include all patients who are randomised and who have at least one post-baseline assessment of NPCCSS. This will be used as the primary analysis set for efficacy.

A Per Protocol (PP) set will also be used to present efficacy data. This will include only patients who have taken at least 80% of their randomised medication up to the 6-month assessment, and have an assessment at 6 months or beyond (it will exclude all patients with less than 6 months of follow up data). The 80% of medication criterion will be reviewed and re-confirmed at the time of the blind review of the database. Patients without a confirmed diagnosis of NPC, according to the study inclusion criteria, will also be excluded from the PP analysis set. Patients who receive the wrong treatment in error will be excluded from these efficacy analyses.

A Completers Analysis Set (CAS) will also be used to present efficacy data. This will include only patients who have taken at least 80% of their randomised medication up to the 12-month assessment and have, as a minimum, assessments at baseline and at 12 months (+/-8 weeks). Patients without a confirmed diagnosis of NPC, if any, will also be excluded from the CAS. Patients who receive the wrong treatment in error will be excluded from these efficacy analyses.

- The safety set will include all patients who receive any IMP, regardless of whether that was their correct medication, or not. The safety set will be used for all safety analyses.

The precise details of how the safety data will be presented for the under 12-year olds will be described in the SAP.

20.3. BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarised:

- Demographics (date of birth, sex and race);
- Medical history (including concomitant diseases);
- NPC disease history (NPC-cdb disease history data) including date of initial NPC diagnosis, data of fillipin staining result (if applicable), cholestane triol/oxysterols (if applicable), DNA disease confirmation (date, mutation/s), date of first NPC symptom(s) (and description), history of neurological manifestations and past treatments.

20.4. EVALUATION OF PRIMARY ENDPOINT

The primary analysis is by a general linear mixed model for repeated measurements. The primary endpoint is 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 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 model allows for the calculation of the 95% confidence interval (CI) for the treatment effect, and a *P*-value to test the null hypothesis that the effect of arimoclomol and placebo is the same.

20.5. EVALUATION OF SECONDARY ENDPOINTS

Key Secondary Endpoints:

- *Responder analysis of patient's CGI-I score remains stable or shows improvement at 12 months and descriptive summary of responder rate at 12 months.*
- *Responder analysis of patient's 5 domain NPCCSS score remains stable or improves at 12 months and descriptive summary of responder rate at 12 months.*

These will be analysed at 12 months using two-tailed chi-squared tests. 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.

- *Time to worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS)*

Kaplan-Meier plots for time to worsening will be produced for each treatment group and compared via a log-rank test, stratified for use of miglustat.

- *Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 6 and 12 months*
- The proportions of patients who have shown worsening by 6 months and by 12 months will be analysed using two-tailed chi-squared tests on the FAS and will be repeated for the PP set and the CAS. 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. *Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) from baseline to 12 months*: This will be analysed using an analysis of covariance model including baseline full scale NPCCSS score (apart from hearing domains), miglustat and randomised treatment as the only covariates.

<u>Other Secondary Endpoints</u>

- *Change in 5 domain NPCCSS at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* The change in 5 domain NPCCSS at 6 months will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months. Data from 18 months and beyond will be summarised descriptively.
- *Change in full scale NPCCSS score apart from hearing domains (i.e. Hearing and Auditory Brainstem Response) at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months*: This will be analysed descriptively.
- *Responder analysis of the CGI-I score remains stable or shows improvement at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months.*
- *Responder analysis of 5 domain NPCCSS score remains stable or improves at 6 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months*.
- *Proportion of patients worsening (as defined by reaching the MCID on patient's 5 domain NPCCSS) at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.*
- *Changes in each individual domain of the NPCCSS at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* These will be tabulated and presented descriptively, including each domain score and its change from baseline.
- *Change in the NPC-cdb score (modified "Stampfer Score") at 6, 12 and 18 monts and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months.
- *Change in Quality of Life (EQ 5D Y) at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* The changes from baseline will be simply compared by a Mann Whitney (independent samples) test and 95% CI at each of 6 and 12 months). Data from 18 months and every 6 months thereafter until End of Extension Phase at 60 months will be summarised descriptively.

- *Change in the SARA score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months.
- *Change in the 9HPT time at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed using the same model as for the change in the full NPCCSS (apart from hearing domains) at 6 months.
- *CGI-S score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed descriptively showing the distribution of scores for each treatment group at 6 and 12 months and the overall distribution of scores at 18 months and every 6 months thereafter until End of Extension Phase at 60 months.
- *CGI-I score at 6, 12 and 18 months and every 6 months thereafter until End of Extension Phase at 60 months:* This will be analysed descriptively showing the distribution of scores for each treatment group at 6 and 12 months and the overall distribution of scores at 18 months and at every 6 months thereafter until End of Extension Phase at 60 months.

20.6. EVALUATION OF EXPLORATORY ENDPOINTS

- *NPC disease progression rate based on the NPCCSS (apart from hearing domains) from baseline in the CT-ORZY-NPC-002 study to 6 and 12 months.* This will be analysed using a similar model as for the change in the NPCCSS score at 6 months. Specifically, the analysis of covariance models (2 models) will have as response variables: rate of disease progression between Baseline and (1) 6 months in the CT-ORZY-NPC-002 study and (2) 12 months in the CT-ORZY-NPC-002 study. The covariates in each model (the same in both analyses) will be rate of disease progression in study CT-ORZY-NPC-001, miglustat use, and randomised treatment.
- *The number of patients leaving the blinded phase of the study before 12 months as a result of early escape* will be presented.
- *The number of patients who either withdraw from the study before 12 months, or who need to jump to escape therapy* will be presented.
- *Change in use of NPC medication/standard of care (including miglustat therapy) at 12, 18 months and every 6 months thereafter until End of Extension Phase at 60 months* will be listed.

Point estimates of treatment differences with 95% CIs and proportions of treatment difference with 95% CIs will be presented for each subgroup where applicable. Exploratory subgroup analyses will be performed based upon:

- Use (or not) of miglustat at randomisation, age;
- 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), genotype, at baseline divided into 3 severity groups <4, 4-22 and change in>22;
- Disease severity defined as the full scale NPCCSS, (apart from hearing domains) score at 3 months (baseline divided into tertiles; 0 - ≤18, 19 - ≤36, 37 - ≤54);
- Change in full scale NPCCSS score, (apart from hearing domains) from baseline) to 3 months for patients with late infantile phenotype (age at the start of neurological symptoms: from (at age 2 years up to and including <6 years old).

20.7. MISSING DATA AND SENSITIVITY ANALYSES

All reasons for missing data will be documented.

Any patient with missing baseline NPCCSS data will have the median for all patients imputed. It is not expected that any patient will have this baseline missing.

As a first analysis accounting for missing data, a multiple imputation approach will be taken, 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).

The method described above assumes that the missing values are “missing at random” (MAR); that is, the probability that an observation is missing may depend on the *observed* data, but not on the *missing* data. This is particularly important to account for patients who progress quickly who need to jump to the “escape” section of the protocol and for whom their heightened disease severity will be recorded (and form the reason for them to jump to the escape therapy).

As a second analysis accounting for missing data, a non-parametric approach will be taken, 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.

For the clinical global impression of severity (CGI-S) at 6 and 12 months, the cumulative distribution of total NPCCSS scores apart from hearing domains (probability of attaining each score level, or worse) will be plotted, stratified by patients in each clinical global impression category and by treatment.

Cumulative distribution plots for clinical global impression of improvement (CGI-I) from baseline to 6 and 12 months will be plotted similarly.

All efficacy analyses (using and not using missing data imputation methods) will be repeated and presented using the PP analysis set and CAS, as defined in Section 20.2.3 and to be reviewed and confirmed in the blind review of the SAP.

20.8. EVALUATION OF CLINICAL STATUS

The clinical status parameters listed in Section 14.1 will be summarised.

20.9. EVALUATION OF SAFETY

The safety parameters are listed in Section 15.1.

All AEs will be displayed in summary tables, by MedDRA system organ class and preferred term. Other safety data (including laboratory data) data will be summarised using appropriate descriptive statistics.

20.10. EVALUATION OF IMAGING

The imaging parameters listed in Section 16.1 will be summarised.

20.11. EVALUATION OF PHARMACOKINETICS

The PK parameters listed in Section 17.1 will be summarised. POP PK will also be modelled and analysed separately to the clinical study report.

20.12. EVALUATION OF BIOMARKERS

The biomarker parameters listed in Section 18.1 will be summarised.

20.13. EVALUATION OF OTHER ENDPOINTS

The parameters other endpoints as listed in Section 19.1 will be summarised.

20.14. INTERIM ANALYSIS

Two interim analyses are planned. One will be carried out after all ongoing patients have received 12 months of blinded treatment and another will be carried out after all ongoing patients have received 12 months of open-label treatment with arimoclomol. An interim analysis may be performed prior to completion of the trial to support a potential regulatory submission.

21. OBLIGATIONS OF THE PRINCIPAL INVESTIGATOR

The study will be performed in accordance with:

- The protocol;
- The Declaration of Helsinki (WMA, 2013);
- International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) (ICH E6(R2), 1996);
- All local regulations.

21.1. INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD

It is the responsibility of the Investigator to obtain approval of the trial protocol/amendments from the IEC/IRB. Prior to the initiation of the study, the Investigator/Worldwide Clinical Trials will submit the following documents to the appropriate IECs/IRBs for approval:

- The study protocol and any amendments;
- The PICD and any other written documents to be provided to the patient (and the patient's parent[s]/legal guardian[s]);
- The IB;
- Details of any compensation to patients;
- The current *Curriculum Vitae* of the Principal Investigator;
- Any other requested document(s).

A copy of the approval will be sent to Worldwide Clinical Trials along with all other correspondence with the IEC/IRB, including the submission documents. The Investigator should file all correspondence with the IEC/IRB in the Investigator Site File.

The study will not start until approval of the protocol and the PICD has been obtained from the appropriate IEC/IRB. The letter of approval should be dated and should specify the protocol number and date of the protocol or amendment which was reviewed and approved. It should also specify the date of the PICD that was reviewed and approved.

A dated list of the voting members of the IEC/IRB who were present when the protocol was reviewed and approved, including their titles/occupations and institutional affiliations should be provided where possible by the Investigator to Worldwide Clinical Trials prior to study initiation. The Investigator will make all attempts to ensure that the IEC/IRB is constituted and operates in accordance with the ICH-GCP and any local regulations.

The Investigator will submit any protocol amendments to the IEC/IRB (and other local authorities, according to local regulations) prior to implementation.

The Investigator will submit required progress reports to the IEC/IRB that approved the protocol at least annually, as well as report any SAEs, life-threatening problems or deaths, to comply with ICH-GCP. The Investigator must inform the IEC/IRB of the termination of the study.

21.2. REGULATORY BODY APPROVAL

The study will not be started until Worldwide Clinical Trials has received approval from relevant regulatory bodies. Worldwide Clinical Trials will provide the Investigator with a copy of the relevant document on behalf of the Sponsor.

21.3. INFORMED CONSENT AND SCREENING DATA

PICDs (including patient assent as per local laws and regulations) will normally be based on a master document provided by CRO or the study Sponsor and must be approved by the study Sponsor prior to submission to the IEC/IRB. The content of the PICD should reflect that described in Section 4.8.10 of the ICH Guidelines and any local requirements e.g. IEC/IRB. Any changes requested by the IEC/IRB must be approved by study Sponsor prior to the documents being used. A copy of the final, IEC/IRB-approved consent form must be submitted to the CRO prior to initiation of this study. The Investigator should file the signed PICDs for review by Worldwide Clinical Trials CRAs.

Written informed consent (and assent as per local laws and regulations) will be obtained from each patient (and/or their parent[s]/legal guardian[s]) prior to inclusion in the trial, and prior to any study-related assessments are performed, as described in Sections 10.1.

21.4. CASE REPORT FORMS AND SOURCE DOCUMENT VERIFICATION

CRFs/eCRFs of a design mutually agreed upon by the Sponsor and delegate(s) will be supplied to the sites. CRFs/eCRFs are the sole property of KemPharm Denmark A/S and should not be made available in any form to third parties, except for authorised representatives of appropriate Health/Regulatory Authorities, without written permission from KemPharm Denmark A/S.

A CRF/eCRF is required and should be completed for each included (consented) patient. The Investigator will be responsible for the accuracy of the data entered into the CRF/eCRF. All data must be entered in English and must be completed by designated study personnel. The completed CRFs/eCRFs must be reviewed, and (electronically for eCRFs) signed/dated by the Investigator in a timely fashion. If a change is made on any of the eForms/CRF pages after the Investigator has signed that eForm/CRF, the Investigator must re-sign the eCRF/CRF.

The relevant completed eForms must be available for review to designated Worldwide Clinical Trials representatives at each scheduled monitoring visit.

The Investigator will allow designated Worldwide Clinical Trials representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the CRFs/eCRFs.

Source documents (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial. Source documents should be available to support all the data recorded in the CRF/eCRF. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient included in this clinical trial.

21.5. CONFIDENTIALITY

Personal data of the patient shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorised or unlawful processing and against accidental loss, destruction or damage and by using appropriate technical or organisational measures. One such measure is by the Investigator ensuring that the patients' personally identifiable information is replaced through the use of pseudonymisation.

On the eCRFs or other documents submitted to Worldwide Clinical Trials, patients will NOT be identified by their names but by the assigned patient number and their initials to ensure confidentiality of the patients' information and that data minimisation principles are maintained.

If patient names are included in error on copies of documents submitted to Worldwide Clinical Trials, the names (except for initials) will be erased or securely destroyed and the assigned patient number added to the document.

The Investigator should keep a separate log (Patient Master List) of patient's codes (assigned patient number), names, addresses, telephone numbers and hospital numbers (if applicable). Documents not intended for submission to Worldwide Clinical Trials (e.g. signed consent forms, completed Patient Master List, etc.) should be maintained by the Investigator in strict confidence and not disclosed to any parties outside of this approved agreement. eCRFs should be protected by use of strong encryption.

21.6. STAFF INFORMATION AND RESPONSIBILITIES

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed to allow collection of accurate, consistent, complete and reliable data.

The Investigator will provide a list of delegated responsibility to Worldwide Clinical Trials, detailing the various study tasks to be performed by each member of his/her study staff. Each staff member should sign in agreement to their performing each of the tasks delegated to them on the list. Worldwide Clinical Trials should ensure that the staff have the required knowledge and training for the tasks delegated to them.

21.7. ESSENTIAL DOCUMENT RETENTION

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while ensuring confidentiality of the trial patients' personal data. Documents that enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and show whether the trial is, or has been, conducted in accordance with ICH-GCP and applicable regulatory requirements are considered essential documents.

The Investigator will retain copies of all the essential documents (as defined by ICH-GCP) until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. The period of document retention is, however, also dependent on the applicable regulatory

requirements (e.g. EEC Directive 91/507 requires retention of patient codes for at least 15 years after the completion or discontinuation of a trial and retention of hospital records and other source data for the maximum time permitted by the institution where the study takes place). The Investigator should take measures to prevent accidental or premature destruction of these documents.

The essential documents include: the signed protocol, copies of the completed CRFs/eCRFs, signed PICDs from all patients (and/or the patient's parent[s]/legal guardian[s]) who consented, hospital records and other source documents, IEC/IRB approval and all related correspondence, including approved documents, and all other documentation included in the Investigator Site File.

The Investigator will inform the Sponsor of the storage location of these essential documents and must contact the Sponsor before disposing of any. If the Investigator wishes to assign the files to someone else (e.g. if he/she retires) or to remove them to another location, the Sponsor Project Manager should be consulted about this change.

The Sponsor will inform the Investigator in writing when these documents no longer need to be retained.

22. STUDY MANAGEMENT

22.1. MONITORING

Prior to study commencement, the Investigator will be informed of the anticipated frequency of the monitoring visits. He/she will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or his/her Sub-investigator(s) and other appropriate staff will be available on the day of the visit to discuss study conduct. Worldwide Clinical Trials is responsible for ensuring the proper conduct of the clinical trial with regards protocol adherence and validity of the data recorded in the CRFs/eCRFs.

A site initiation visit **must** be conducted by the CRO and the site must be activated prior to the commencement of any study activities requiring informed consent (i.e. any invasive screening tests).

22.2. QUALITY ASSURANCE AND QUALITY CONTROL

An independent audit of the study may be conducted during the study or after completion. The audit may be conducted by either Worldwide Clinical Trials or the Sponsor's Quality Assurance (QA) department or an independent auditor or a regulatory authority.

22.2.1. Quality Control

Quality Control (QC) is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled.

QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

22.2.2. Quality Assurance

Quality Assurance (QA) is defined as the planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

22.2.3. Audit

The Investigator will permit an audit mandated by the Sponsor after reasonable notice. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of patients enrolled have been protected and that all data relevant for the evaluation of the IMP have been captured, processed and reported in compliance with the planned arrangements. The Investigator will permit direct access to all study documents, IMP accountability records, medical records and source data. The Investigator and his/her study team will also be available for discussion regarding study progress and procedures during the audit (both during the audit and at the end of the audit for an "exit" discussion).

22.3. DATA QUERY PROCESS

Sites will enter the data from source documents into the eCRF/CRF in timely manner and the data will be verified for missing data, inconsistencies, and for any necessary medical clarifications. Queries arising from these checks will be flagged within the eCRF or by data clarification/query forms. The site staff will correct, confirm or clarify the data as appropriate. All possible attempts should be made by the site staff to resolve the queries within the requested timeframes. If the site staff are unsure about the meaning of a query, or what data is required, then they should seek clarification from the Worldwide Clinical Trials CRA assigned to their site.

Once all data queries have been resolved, the study will be declared to be "clean", and the eCRF will be locked ready for statistical analysis. After clean-file status has been achieved, Worldwide Clinical Trials will provide copies of each patient's eCRF to the Investigator for archiving. Copies of each patient's eCRF/CRF will also be archived by the Worldwide Clinical Trials.

The data management, data handling, and analysis will be conducted in accordance with good clinical, scientific and data management principles and in compliance with the Standard Operating Procedures of the relevant KemPharm Denmark A/S delegates.

22.4. PROTOCOL DEVIATIONS/AMENDMENTS

The trial must be conducted in accordance with:

- The protocol;
- Applicable regulatory requirement(s) or conditions linked to the approval(s) of the study;
- Applicable IEC/IRB requirement or conditions linked to the approval(s) of the study;
- Any particulars or documents, other than the protocol, accompanying the regulatory or IEC/IRB request or that application.

Any deviation from the protocol that has not been approved by KemPharm Denmark A/S and the IEC/IRB could result in a discontinuation from the study at the site involved. Any amendment(s) to the protocol must be approved by both KemPharm Denmark A/S and the IEC/IRB which granted the original approval of the study prior to their implementation (unless only logistical or administrative aspects of the trial are involved). All substantial amendments to the protocol must be approved by the applicable regulatory bodies prior to their implementation.

However, in the event of any medical emergency, the Investigator is free to institute any medical procedure he/she deems appropriate. Such events and procedures must be promptly reported to the KemPharm Denmark A/S and Worldwide Clinical Trials representatives.

22.5. DISCONTINUATION OF THE STUDY

KemPharm Denmark A/S reserves the right to stop the study at any time on the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other valid administrative reasons. After such a decision is made, the Investigator must inform all patients being screened or followed up as soon as possible. All delivered study materials must be collected and all CRFs/eCRFs completed to the extent possible.

22.6. PUBLICATIONS

The study will be registered at www.clinicaltrials.gov. By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications and extent of involvement. Except for legal reasons, the Investigators will not reveal the result of the study to a third party whilst the data is not yet in the public domain without a mutual agreement about the analysis and interpretation of the data with KemPharm Denmark A/S.

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the study (including ancillary study involving trial patients) must be prepared in conjunction with KemPharm Denmark A/S and must be submitted to the KemPharm Denmark A/S for review and comment at least 6 weeks prior to submission for publication or presentation.

Authorship credit should be based on substantial contributions to conception and design, acquisition of data, or analysis and interpretations of data; and be decided by KemPharm Denmark A/S and the international coordinating Investigator in cooperation. KemPharm Denmark A/S has all editorial rights of the data from this study.

23. STUDY TIMETABLE

- Planned start of the study (first patient in [FPI]): Q2 2016
- Planned end of the main study (12-month blinded phase): Q2 2018
- Planned end of the extension phase (48-month follow up): Q2 2022

The end of the study is defined as the last visit of the last patient.

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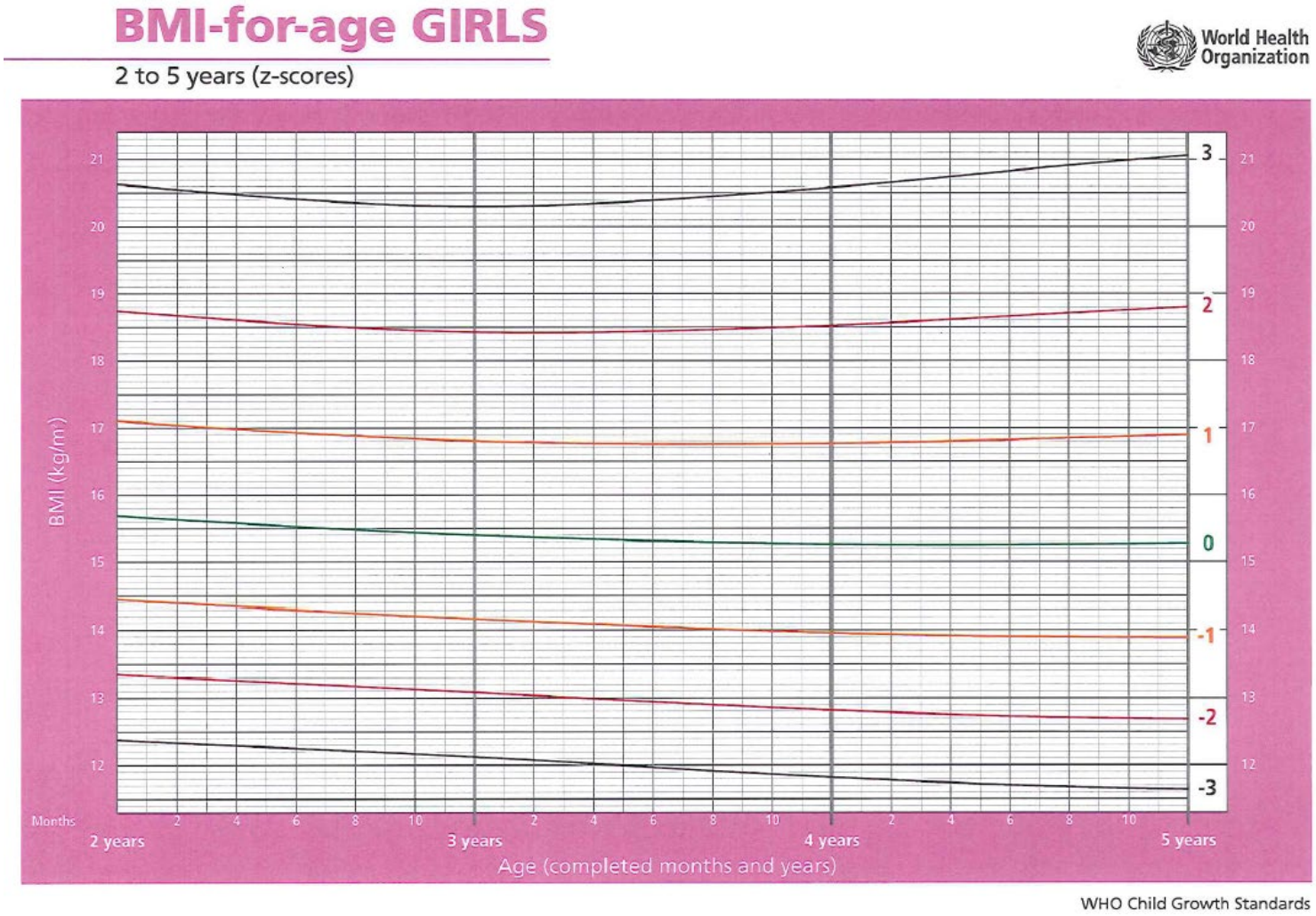
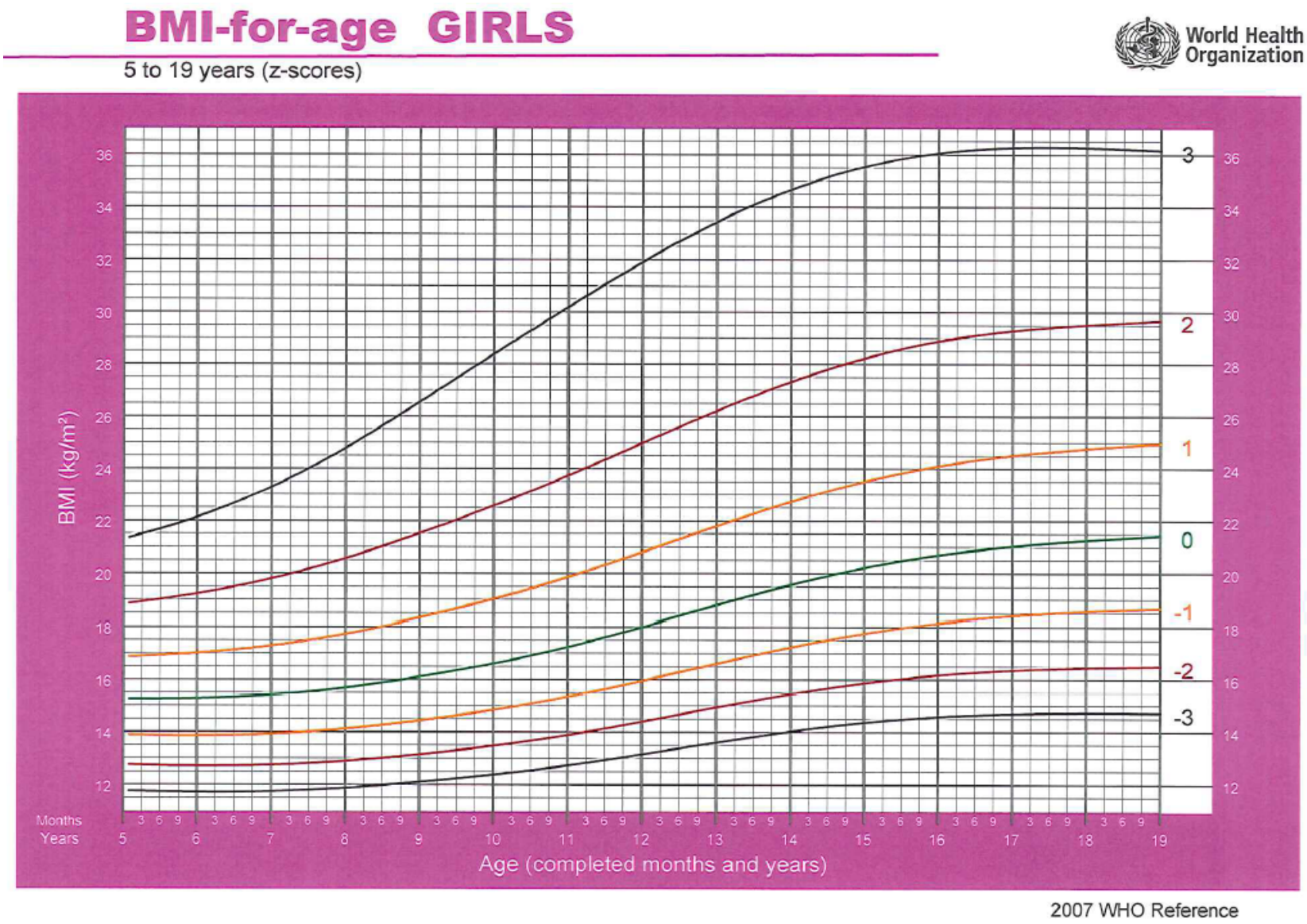
25. APPENDICES

25.1. APPENDIX I: BMI FOR AGE - WORLD HEALTH ORGANISATION




BMI-for-age GIRLS
5 to 19 years (z-scores)
World Health Organization
BMI (kg/m²)
36
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14
12
3
2
1
0
-1
-2
-3
Months
Years
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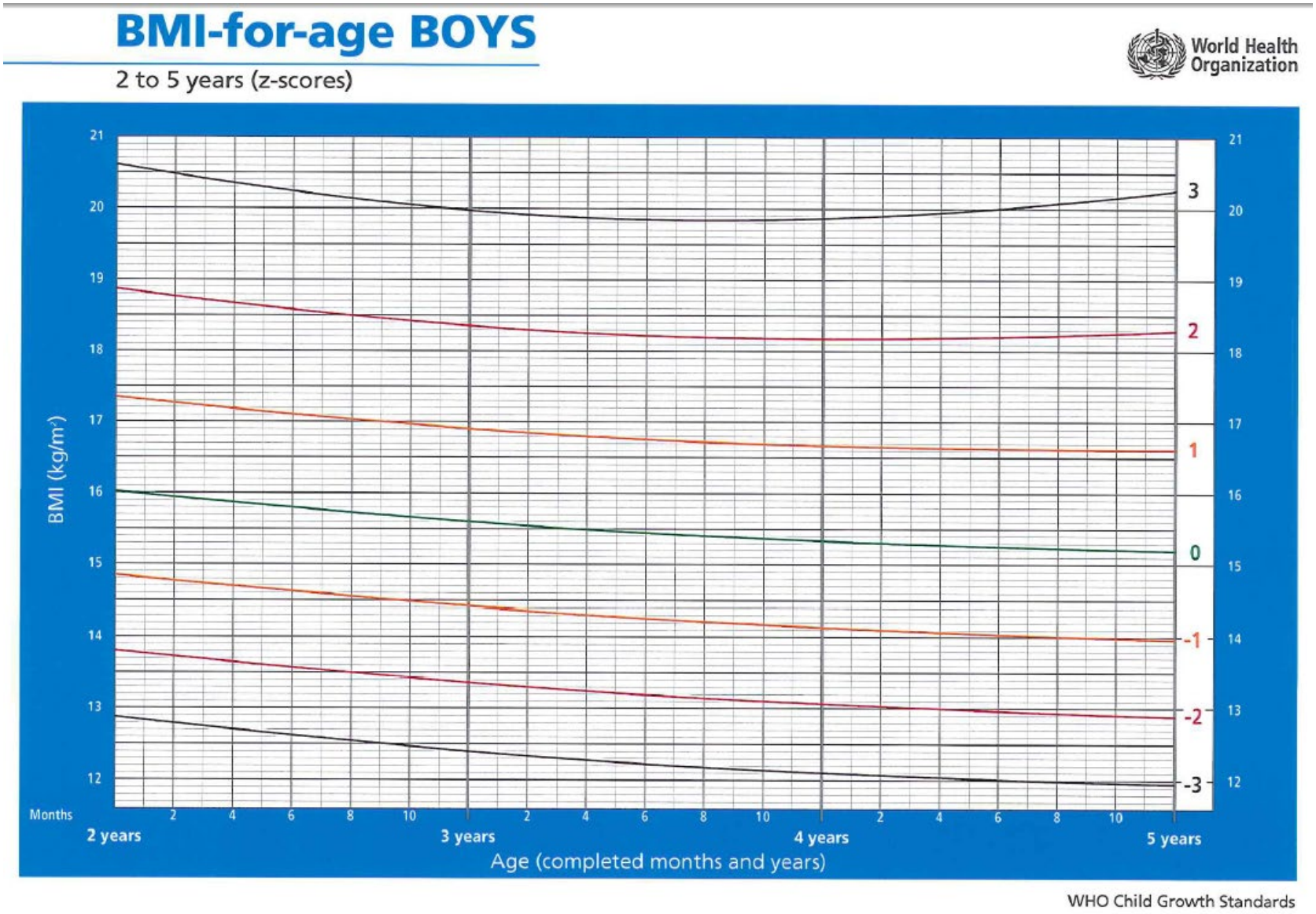
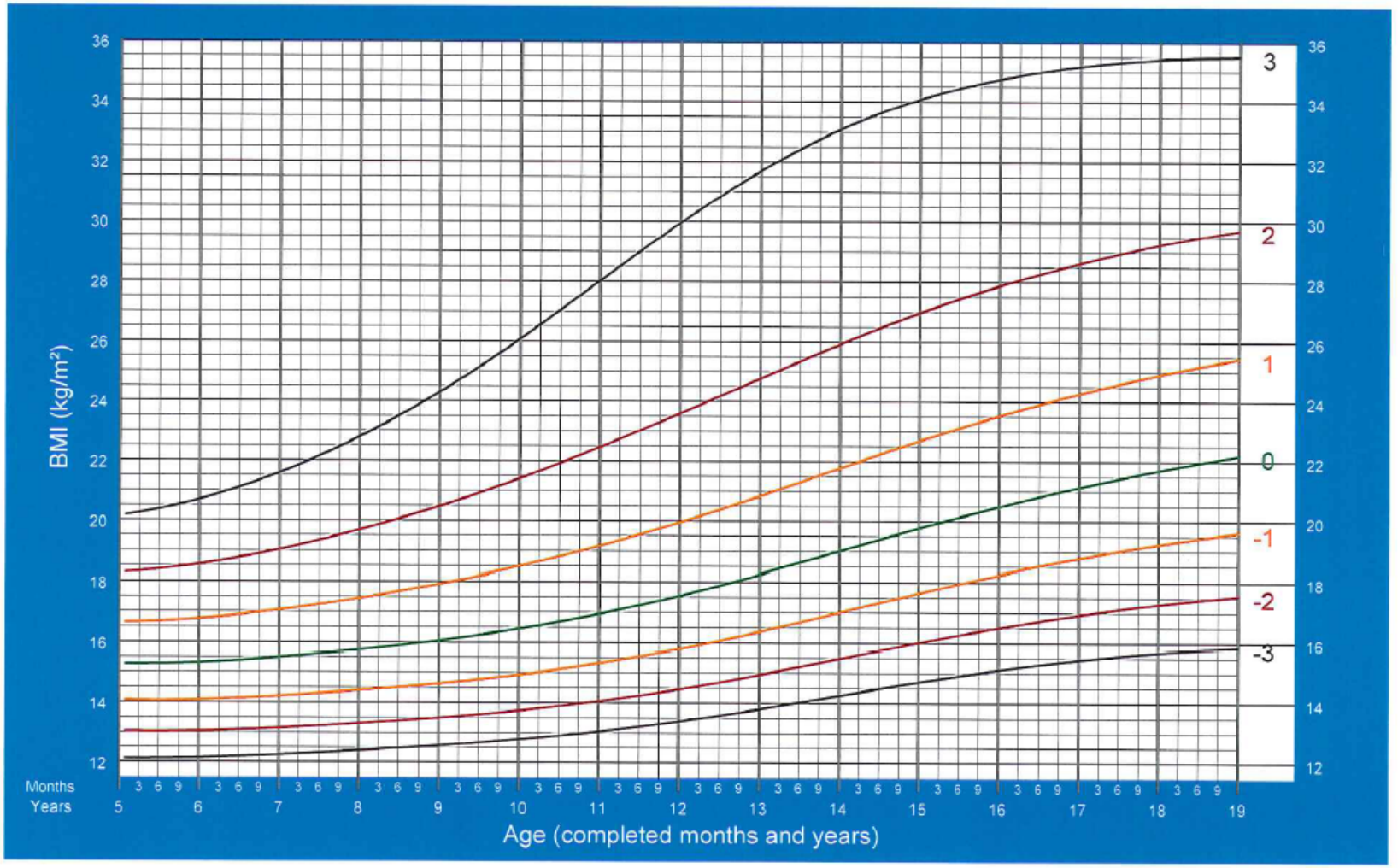
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Age (completed months and years)
2007 WHO Reference


BMI-for-age BOYS
2 to 5 years (z-scores)
World Health Organization
BMI (kg/m²)
21
20
19
18
17
16
15
14
13
12
3
2
1
0
-1
-2
-3
Months
2 years
3 years
4 years
5 years
Age (completed months and years)
WHO Child Growth Standards


BMI-for-age BOYS
5 to 19 years (z-scores)
World Health Organization
BMI (kg/m²)
36
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Age (completed months and years)
2007 WHO Reference

25.2. APPENDIX II: STUDY FLOW CHART: 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	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 occur 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.

y **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.

[z] **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.

25.3. APPENDIX III: STUDY FLOW CHART: 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	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 occur 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.

25.4. APPENDIX IV: STUDY FLOW CHART: EXTENSION PHASE: ALL PATIENTS

STUDY PHASE	FOLLOW-UP				
	Visit 7	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
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	42 months (±8 weeks) after randomisation
Physical examination[a]	X	X	X	X	X
Weight	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X
Haematology[c]	X	X	X	X	X
Clinical Chemistry[d]	X	X	X	X	X
POP PK Sampling[e]		X			
Blood Sample for Biomarker Analysis[f]	X	X	X	X	X
Pregnancy test[g]	X	X	X	X	X
NPCCSS[h]	X	X	X	X	X
NPC-cdb score[i]	X	X	X	X	X
SARAj[i]	X	X	X	X	X
9HPT[j]	X	X	X	X	X
CGI-S & CGI-I[j]	X	X	X	X	X
Quality of Life Scoring[j]	X	X	X	X	X
Concomitant Therapy[k]	X	X	X	X	X
Adverse Events[l]	X	X	X	X	X
Arimoclomol Dispensing[m]	X	X	X	X	X
Arimoclomol Return[m]	X	X	X	X	X
Arimoclomol Administration[n]	X	X	X	X	X
Telephone Follow up[o]	X (every 3-4 months)				

APPENDIX IV: STUDY FLOW CHART: EXTENSION PHASE: ALL PATIENTS (CONTINUED)

STUDY PHASE	FOLLOW-UP		END OF EXTENSION PHASE[q]	UNSCHEDULED VISIT[p]
	Visit 12	Visit 13	Visit 14	NA
PROCEDURES	48 months (±8 weeks) after randomisation	54 months (±8 weeks) after randomisation	60 months (±8 weeks) after randomisation or within 4 weeks of withdrawal during extension phase	NA
Physical examination[a]	X	X	X	
Weight	X	X	X	X
Vital Signs[b]	X	X	X	
Haematology[c]	X	X	X	X
Clinical Chemistry[d]	X	X	X	X
POP PK Sampling[e]				(X)
Blood Sample for Biomarker Analysis[f]	X	X	X	
Pregnancy test[g]	X	X	X	
NPCCSS[h]	X	X	X	X
NPC-cdb score[i]	X	X	X	
SARA[j]	X	X	X	
9HPT[j]	X	X	X	
CGI-S & CGI-I[j]	X	X	X	
Quality of Life Scoring[j]	X	X	X	
Concomitant Therapy[k]	X	X	X	X
Adverse Events[l]	X	X	X	X
Arimoclomol Dispensing[m]	X	X		X
Arimoclomol Return[m]	X	X	X	X
Arimoclomol Administration[n]	X	X		X
Telephone Follow up[o]	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. **POP PK Sampling**: POP PK sampling will be performed for all patients as follows:

Visit 8 and unscheduled visit: 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.

POP PK sampling at the unscheduled visit is at the discretion of the Investigator.

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

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

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

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

j. **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).

k. **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.

l. **Adverse events (AEs)**: ALL AEs which occur 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.

m. **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.

n. **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.

o. **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.

p. **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.

q. **End of Extension Phase**: The end of extension phase visit should take place within 60 months (±8 weeks) after randomisation or within 4 weeks of withdrawal during 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.

25.5. APPENDIX V: PAEDIATRIC SUBSTUDY

The sub-study is ongoing as a separate trial and does not contribute to the primary or secondary endpoints of the main trial. Therefore the details are not included here.