**CLINICAL TRIAL PROTOCOL**

Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C: A multinational, multicenter, open-label, rater-blinded Phase II study.

| | |
|---|---|
| Protocol Number: | IB1001-201 |
| Investigational Medicinal Product: | N-Acetyl-L-Leucine (IB1001) |
| Indication: | Niemann-Pick disease type C (NPC) |
| Phase: | II |
| SPONSOR: | IntraBio Ltd. [redacted] |
| US LEGAL REPRESENTATIVE: | IntraBio Inc [redacted] |
| EU LEGAL REPRESENTATIVE: | IntraBio Ireland Ltd [redacted] |
| EUDRACT Number: | 2018-004331-71 |
| IND Number: | 134369 |
| Protocol Version and Date: | Version 7.0, 10-Oct-2022 |

*The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.*

**Protocol Approval**

**Sponsor:**
IntraBio Ltd.
[redacted]

_____ _____
Signature Date

**Medical Monitor:**
[redacted]

_____ _____
Signature Date

**Biostatistician:**
[redacted]

_____ _____
Signature Date

**Principal Investigator Agreement**

I, _____, (Investigator's Name) have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

The information contained in this protocol is provided to me in confidence, for review only by myself, the ethics committee authorized to review and approve the trial at this trial site, and designated trial staff participating in this clinical study.

I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval by the trial Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the investigational medicinal product (IMP), N-Acetyl-L-Leucine, and the conduct of the trial.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this trial.

I agree to carry out all terms of this protocol in accordance with the ICH GCP (Good Clinical Practice) Guidelines, the Declaration of Helsinki and local regulations. I will ensure that the Investigational Medicinal Product is used only as described in the protocol or any subsequent amendment.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorisation from the trial Sponsor except to the extent necessary to obtain informed consent from potential trial patients.

_____ _____

Investigator's Signature Date

_____

Clinical Trial Site Name

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | | |
|---|---|---|
| **Document** | **Protocol Version** | **Date** |
| Amendment 5 | Version 7.0 | 10-Oct-2022 |
| Amendment 4 – Slovakia Version | Slovakia Version 6.2 | 07-Dec-2020 |
| Amendment 4 – US Version | US Version 6.1 | 26-Aug-2020 |
| Amendment 4 | Version 6.0 | 25-Aug-2020 |
| Amendment 3 – US Version | US Version 5.1 | 14-Dec-2019 |
| Amendment 3 | Version 5.0 | 14-Nov-2019 |
| UK Amendment 1 | Version 2.1 | 07-Oct-2019 |
| Amendment 2 | Version 4.0 | 28-Aug-2019 |
| US Specific Amendment 1 | Version 3.0 | 27-Jan-2019 |
| Global Protocol Version 2 (Original Protocol Submitted) | Version 2.0 | 11-Dec-2018 |
| Global Protocol Version 1 | Version 1.0 | 4-Dec-2018 |

The Summary of Changes is located in the supplementary document, “IB1001-201 Protocol Summary of Changes Version 2.0, 10-Oct-2022”.

**PROTOCOL SYNOPSIS**

Included as Appendix 1.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| 8MWT | 8-meter walk test |
| 9HPT-D | 9-hole peg test of the dominant hand |
| 9HPT-ND | 9-hole peg test of the non-dominant hand |
| AE | Adverse event |
| AEMPS | Spanish Agency of Medicines and Medical Devices |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomic Therapeutic Chemical |
| CFR | Code of Federal Regulations |
| CGI | Clinical global impression |
| CGI-C | Clinical global impression of change |
| CGI-S | Clinical global impression of severity |
| CHMP | Committee for Medicinal Products for Human use |
| CHO | Chinese hamster ovary |
| CI-CS | Clinical impression of change in severity |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case report form |
| CS | Clinically significant |
| CI-S | Clinical impression of severity |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EQ | EuroQol |
| ET | Early termination |
| FAS | Full analysis set |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transpeptidase |
| GMP | Good manufacturing practice |
| ICF | Informed consent form |
| ICH | International Council on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| ITT | Intention-to-treat |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone releasing system |
| LAM | Lactational amenorrhoea method |
| LOCF | Last observation carried forward |
| MASAP | Meta-analysis statistical analysis plan |
| mDRS | Modified disability rating scale |
| MEB | Dutch Medicines Evaluation Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | United Kingdom Medicines and Healthcare Products Regulatory Agency |
| mITT | Modified intention to treat |
| MoCA | Montreal Cognitive Assessment |
| NCS | Not clinically significant |
| NPC | Niemann-Pick disease type C |
| NPC-CSS | NPC clinical severity scale |
| PI | Principal investigator |
| PK | Pharmacokinetic(s) |

| | |
|---|---|
| PPS | Per protocol set |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical Analysis Plan |
| SARA | Scale for the assessment and rating of ataxia |
| SCAFI | Spinocerebellar ataxia functional index |
| SD | Standard deviation |
| ULN | Upper limit of normal |
| US | United States |
| VAS | Visual analogue scale |
| WHO | World Health Organization |

# 1 INTRODUCTION

The goal of this study is to demonstrate that N-Acetyl-L-Leucine is efficacious in improving symptoms, functioning, and quality of life against the defined endpoints in patients with Niemann-Pick Type C disease (NPC) for the purpose of establishing the benefit/risk balance of investigational medicinal product in the proposed clinical setting.

NPC is a rare, devastating, neurovisceral autosomal-recessive inherited metabolic, lysosomal storage disorder (LSD) that predominantly affects pediatric patients [Vanier, 2010; Utz et al, 2017]. In general, patients with neurological onset early in life have more severe symptoms, deteriorate faster, and die sooner [Wraith et al, 2009]. NPC is estimated to affect 1:100,000 live births [Vanier, 2010].

There are limited and no curative treatments approved for NPC worldwide, and no approved treatments in the United States. Therefore, there is a strong need for the development of novel and more effective therapies to treat these intractable diseases.

N-Acetyl-L-Leucine is the L-enantiomer of N-Acetyl-DL-Leucine, a modified amino acid that has been available in France since 1957 under the trade name Tanganil® (Pierre Fabre Laboratories) as a treatment for acute vertigo and is available as a solution for injection and as a tablet. N-Acetyl-L-Leucine is not currently authorized anywhere in the world for the treatment of any condition.

The Sponsor's (IntraBio Ltd.) development of Acetyl-Leucine for NPC began with the investigation of the commercially available racemic mixture, N-Acetyl-DL-Leucine (Tanganil®). IntraBio's collaborators reported in a case series on 12 patients with NPC that the modified amino-acid Acetyl-DL-Leucine (3 g/day for one week followed by 5 g per day for three weeks) significantly improved the symptoms of NPC, measured by the Scale for the Assessment and Rating of Ataxia (SARA), the Spinocerebellar Ataxia Functional Index (SCAFI) and EuroQol-5D-5L. N-Acetyl-DL-Leucine was very well tolerated, and no side effects except intermittent dizziness were reported [Bremova et al, 2015]. An additional case series is available in the literature describing the disease modifying effect of long-term treatment with N-Acetyl-DL-Leucine in 10 patients with NPC treated for a median length of 7.7 months (maximum 21.2, minimum 2.7 months) [Cortina-Borja et al, 2018]. In all studies, the compound was well-tolerated with no discernible serious side effects.

Recent *in vitro* and *in vivo* studies have demonstrated that the L-enantiomer mediates the therapeutic effect and has potential clinical benefits over the racemic mixture [Platt, 2018; Mann, 2018]. IntraBio therefore intends to focus further development on N-Acetyl-L-Leucine without the presence of D-enantiomer. The safety profiles of both N-Acetyl-DL-Leucine and N-Acetyl-L-Leucine have been characterized in both preclinical and clinical studies. In addition, the safety profile of N-Acetyl-DL-Leucine has been characterized on the basis of compassionate use experience in NPC (as well as in patients with other lysosomal storage disorders, neurodegenerative and genetic diseases, and further indications).

Based on these findings, IntraBio is conducting this Phase II study investigating the efficacy and safety of N-Acetyl-L-Leucine for the treatment of NPC.

The study drug used in the Parent Study is formulated as 1000 mg Powder for suspension in 40 mL Ora-Blend® and oral administration. Patients aged ≥18 years in the United States and patients aged ≥13 years in Europe will receive a total daily dose of 4 g/day (administered as 3 doses per day). Patients 6 to 12 years of age will receive weight-tiered doses.

Patients will only be included in the study if they meet the inclusion and exclusion criteria described in the study protocol approved by the relevant ethics committees and the regulatory authorities and informed consent is obtained. To further minimize risks, patients will receive the best available clinical care to manage the underlying conditions with careful monitoring of adverse events that may arise during the course of the clinical study.

The overall design of the study is presented and discussed in Section 3.

### 1.1 Risk/Benefit Considerations

NPC is a rare, serious, and life-threatening indication that predominantly affects the pediatric population. Treatment of NPC is so-far limited to symptomatic management and miglustat (Zavesca™) (not approved in the United States). Therefore, there is a strong need for the development of novel and more effective therapies to treat this disease.

The active ingredient in IB1001 is N-Acetyl-L-Leucine, an acetylated derivate of a ubiquitously present amino acid occurring in human food. N-Acetyl-L-Leucine is also an endogenously generated metabolite of L-Leucine.

[redacted]

[redacted]

[redacted]

[redacted]

The racemate, N-Acetyl-DL-Leucine, has been available in France since 1957 under the trade name Tanganil® (Pierre Fabre Laboratories) as an oral treatment for acute vertigo. It has demonstrated very good tolerability. Contraindications are restricted to hypersensitivity to N-Acetyl-DL-Leucine and other ingredients in the Tanganil® formulation. Known side effects are rare cases of skin rash (sometimes associated with pruritus) and urticaria.

A broad set of clinical studies with N-Acetyl-L-Leucine in patients with balance disorders have been conducted, demonstrating the clinical safety of the compound. For N-Acetyl-L-Leucine, two PK studies in 24 (i.v.) and 19 (oral) healthy subjects ([Study No. V00251 IV 101] and [Study No. V00251 ST 101], respectively) have been conducted. Further, the safety of N-Acetyl-L-Leucine was assessed in a multicenter placebo-controlled clinical study conducted in 107 patients (80 patients randomized to N-Acetyl-L-Leucine) with vestibular neuritis [Study No. V00251 IV 201], in which subjects received doses up to 4 g/day i.v. (2 g twice-daily) for 4 days and in a second multicenter placebo-controlled clinical study in 76 patients (50 randomized to N-Acetyl-L-Leucine) with vestibular neuritis [Study No. V00251 ST 201], in which subjects received 8 g/day p.o. for 14 days. The results showed that N-Acetyl-L-Leucine has a good safety profile. It has been further demonstrated that there no interconversion from the L to the D-enantiomers.

Publications on the racemate show N-Acetyl-DL-Leucine to be well tolerated in patients with NPC [Bremova et al, 2015; Cortina-Borja et al, 2018]. In Bremova et al. (2015) patients received N-Acetyl-DL-Leucine for 4 weeks before undergoing a 4-week washout period and in Cortina-Borja et al. (2018) patients were treated with N-Acetyl-DL-Leucine for a median length of 7.7 months (maximum 21.16, minimum 2.7 months). Further information on long-term dosing is provided by an ongoing case series, in which 25 patients with NPC have been dosed with 5 g/day N-Acetyl-DL-Leucine (administered over 3 daily doses) for a minimum of one year and up to over two years, in which N-Acetyl-DL-Leucine was found to be well-tolerated [Dr Michael Strupp, MD, Professor of Neurology LMU Munich, Personal Communication].

From an efficacy point of view, encouraging first data is available from the above studies. Bremova et al. (2015), which compared ataxia symptoms at baseline, after 4 weeks treatment, and after 4 weeks washout, concluded that N-Acetyl-DL-Leucine improved ataxic symptoms and quality of life in patients with NPC. The two case series following individuals receiving N-Acetyl-DL-Leucine ([Cortina-Borja et al, 2018] and [Kaya et al, 2020a]) additionally suggest that N-Acetyl-DL-Leucine slows the rate of disease progression. Pre-clinical studies have also further demonstrated that N-Acetyl-L-Leucine is the active ingredient that medications the long-term, neuroprotective, diseases modifying effect of the racemate, while the D-enantiomer is inactive or potentially antagonistic [Kaya et al, 2020a].

Appropriate patient selection is one factor in considering the balance of risks of adverse events (AEs) against potential clinical benefit. The protocol inclusion and exclusion criteria appropriately consider the patient's overall health and medical history.

Based upon the very good safety profile of N-Acetyl-L-Leucine (and N-Acetyl-DL-Leucine) observed in animals at dose levels up to the limit dose ([redacted]) as well as

**Commented [FP1]:** @Taylor: as discussed with Katharine, this one paragraph is public knowledge and, as such, would not qualify for redaction.

**Commented [TF2R1]:** I disagree - the last 2 paragraphs are but the first are PF data which we explictly cannot share and it has not ever been published, or it is IB's non clinical studies conducted. I left the text in yellow which should be redacted

knowledge of safe use of N-Acetyl-DL-Leucine in children as young as 9 months of age [Picone, 2018], inclusion of children aged 6 years and over is judged to be safe. Women of childbearing potential and partners of women of childbearing potential will be required to adhere to strict precautions to prevent pregnancy. Women who are pregnant, breast-feeding, or planning to become pregnant will be excluded from the study. In addition, a negative pregnancy test will be a prerequisite for the inclusion of women of child bearing potential and urine pregnancy tests will be carried out at approximately 6-weekly intervals throughout the trial.

*Levels of risk and burden on participants*

N-Acetyl-L-Leucine is being developed for the treatment of adults and children with NPC, a rare and ultimately fatal disorder that predominantly affects pediatric patients [Vanier, 2010; Utz et al, 2017]. As described above, published case series and long-term use of N-Acetyl-DL-Leucine in patients with NPC suggest the prospect of a direct benefit to the participating patients over standard of care.

To ensure the feasibility of this trial, NPC clinical experts [redacted] and the heads of multinational NPC patient organizations [redacted] were consulted and involved in its design.

The degree of burden to participants in the study is defined by the description of assessments in Section 7.

The behavioral tests for evidence of efficacy are routinely used in the evaluation of NPC and are relatively fast to perform, with the individual subtests of the SCAFI rarely taking more than 2 minutes for patients with NPC to complete [Bremova et al, 2015]. With regard to the secondary endpoint assessments, the Scale for Assessment and Rating of Ataxia (SARA) takes about 15 minutes and the Niemann-Pick type C Clinical Severity Scale (NPC-CSS) takes about 45 minutes to complete [redacted]. The use of these tests was determined together with representatives of the patient community and parents of patients with NPC and Tay-Sachs disease, as being clinically meaningful for the patients and families and reflective of the ability to perform acts of everyday life safety and securely, while at the same time not being exhausting [redacted].

To minimize blood draws sparse PK sampling will be carried out at the same times that blood is drawn for the safety blood laboratory tests in the Parent Study. Topical anesthesia may be applied before blood sampling. The total amount of blood taken per subject during Parent Study will be approximately 66 mL (42 mL blood for the safety analyses, 24 mL blood for the PK analyses) evenly distributed over the 6 scheduled visits that will take place over a study duration of 14 to 20 weeks. Patients will be ≥15 kg and the total blood volume taken in accordance with the maximum allowable research-related blood sample volumes provided in the incoming EU ethical considerations for clinical trials on medicinal products conducted with minors [EudraLex Volume 10, 2017].

The impact of the interventions will be assessed by patient-reported outcomes (measurement of global impression, see Section 6.1.5, where feasible, and quality of life assessments (EQ-5D-5L and EQ-5D-Y, see Section 6.1.3.

The investigator will monitor the degree of stress to patients and the risk threshold throughout the trial. Patients will be instructed to report any AEs that they experience to the Investigator and the Investigator will ask about the occurrence of AEs at each visit. As described in Section 11.6, if the Investigator (or the Sponsor or Medical Monitor) becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the clinical study may be terminated after appropriate consultation between the involved parties.

In addition, as described in Section 11.5, the Data Safety Monitoring Board (DSMB), in conjunction with the study Medical Monitor and/or Sponsor, will monitor the level of risk on a regular basis throughout the study. The DSMB is a multidisciplinary group consisting of clinicians with pediatric experience and a biostatistician. The DSMB has been set up to safeguard the interests of study participants by providing an independent review of patient safety data to monitor that no undue harm is occurring to patients due to their participation. The DSMB may recommend changes in the conduct of the studies to IntraBio, if needed, to ensure the safety of patients in the study and the proper conduct of the studies. The DSMB may also recommend suspending recruitment or terminate the study early because of undue safety risks to patients or any issues concerning the rights of patients. For this purpose, the DSMB will receive regular updates of safety and review all safety data on a regular basis.

Based upon the nature of the drug, the available non-clinical and clinical data for N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine, the current lack of effective treatments NPC, and in the context of a marketed racemate, this clinical trial is concluded to pose acceptable levels of risk and burden on participants.

### 1.2 COVID-19

This study is ongoing during the COVID-19 epidemic. Coronavirus (COVID-19) outbreaks have been recorded in all countries with study sites and subjects participating in IntraBio's clinical trials and have significantly impacted the IB1001-201 clinical trial.

Protocol Version 5.0 (EU)/ 5.1 (US) was active in countries prior to the widespread outbreak of COVID-19 in the US and Europe. Protocol deviations, urgent safety measures, and modifications to this protocol have been necessary to prioritize and ensure the safety of trial participants, their families, and study site teams, and maintain the integrity of the study.

New or modified processes / contingency measures enacted due to the outbreak of COVID-19 are described throughout the Parent Study Protocol, including a risk/benefit assessment when applicable. All measures and actions that have been implemented due to COVID-19 were first reviewed and agreed by the Data Safety Monitoring Committee (DSMB), the Medical Monitor, and applicable Principal Investigators.

These new or modified processes enacted due to the outbreak of COVID-19 are consistent and permitted per the guidance's issued from applicable regulatory bodies[1] regarding the management of clinical trials in relation to COVID-19. In addition, applicable competent authorities (CA), research ethic committees (REC), and institutional review boards (IRBs) were notified and provided with copies of the applicable guidance's issued by the Sponsor to participating Study Sites regarding the management of the COVID-19 pandemic (including IntraBio 2020a).

*Note: This protocol amendment (Version 6.0 25-Aug-2020) has been made to include changes to protocol procedures which have been enacted due to COVID-19 at this time. However, because COVID-19 is an evolving situation, the ultimate impact of COVID-19 on the IB1001-201 clinical trial remains unknown. Therefore, the protocol and related study documents may be updated as applicable. Any measures implemented in relation to COVID-19 will be in accordance with Guidance's issued from applicable National Competent Authorities. The Data Safety Monitoring Board (DSMB) will also be consulted as applicable to ensure the safety of trial participants and clinical trial site study teams, as well as maintain the integrity of the clinical study. All protocol deviations related to COVID-19 will be well-documented to enable appropriate evaluation of the IB1001-201 clinical trial.*

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective is to evaluate the efficacy of N-Acetyl-L-Leucine based on blinded raters' clinical impression of change in severity (CI-CS) in the treatment of NPC.

## 2.2 Secondary Objective(s)

The secondary objectives are:

- To assess the clinical efficacy of N-Acetyl-L-Leucine on symptoms of ataxia, functioning, and quality of life for patients with NPC;
- To evaluate the safety and tolerability of N-Acetyl-L-Leucine at 4 g/day in patients with NPC, including patients aged ≥18 years in the United States and patients aged ≥13 years in Europe, and weight-tiered doses in patients 6 to 12 years of age in Europe

## 2.3 Exploratory Objective

The exploratory objective is:

- To characterize the pharmacokinetics (PK) of N-Acetyl-L-Leucine in patients with NPC

# 3 OVERALL DESIGN AND PLAN OF THE STUDY

## 3.1 Overview

This study is ongoing during the COVID-19 outbreak. The impact of the global pandemic on the overall design and plan of the study is described in section 3.1.2.5.

### *3.1.1 Trial Design/Patient Population*

This is a multinational, multicenter, open-label, rater-blinded Phase II study that will enroll male or female patients aged ≥6 years in Europe AND ≥18 years in the United States with a confirmed diagnosis of NPC at the time of signing informed consent.

### *3.1.2 Study Design*

Patients will be assessed during three study phases: a baseline period (with or without a study run-in), a treatment period, and a washout period. It is not uncommon for symptoms and functioning to fluctuate over a week, so to help account for intra-patient variability, patients will be assessed twice during each period. Section 7 contains more detailed information on which study assessments and procedures will be conducted for each study phase and visit.

At the initial screening visit, patients will be classified as either "naïve" or "non-naïve" patients depending on their use of prohibited medications within the past 42 days. The schedule of events during the initial screening visit and throughout the baseline period (through **Visit 1**) will vary depending on the patient's classification as either "naïve" or "non-naïve".

#### 3.1.2.1 Baseline Period

***Baseline: "Naïve" Patients*** (Figure 3-1).

(See Appendix 3A for "naïve" patients schedule of events)

"Naïve" patients are defined as patients who, at the initial screening visit, confirm (or whose legal representatives confirm on behalf of the patient) that they have not used any prohibited medications within the past 42 days. For these patients, the initial screening visit will be treated as **Visit 1** (Baseline 1).

A urine sample will be taken at **Visit 1** to detect N-Acetyl-D-Leucine. Provided the patient's levels of N-Acetyl-D-Leucine are below the permitted threshold, the initial screening visit will be confirmed as **Visit 1** (Baseline 1). **Visit 2** (Baseline 2/ Start of treatment period) will take place 14 days (+7 days) after **Visit 1**.

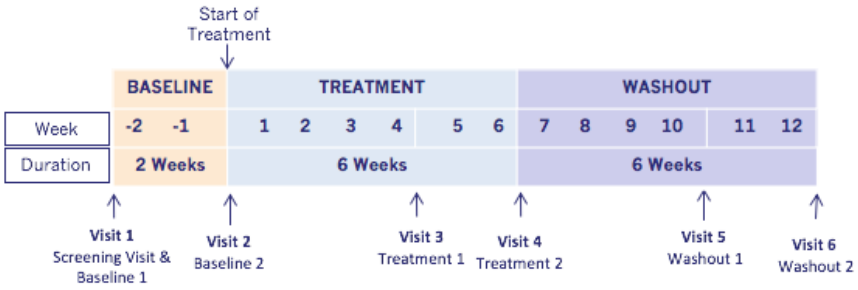


**Figure 3-1: Study Schema for "Naïve" Patients**

***Reclassifying "Naïve" Patients to "Non-naïve" Patients***

**Visit 1** will not be confirmed for "naïve" patients whose urine sample test unexpectedly detects levels of N-Acetyl-D-Leucine above the permitted threshold. Provided the treating physician believes the patient will indeed comply with the pre-treatment washout and complete study the protocol[2], these patients will be given the option to undergo a minimum of 42 days washout before returning for Visit 1 (Baseline 1). Provided the patient (or legal representative on behalf of the patient) consents, the patient will be reclassified as "non-naïve" and will return for a repeat Visit 1 after the study run-in washout period.

***Baseline: "Non-Naïve" Patients*** (Figure 3-2).

*(*See Appendix 3B for "non-naïve" patients schedule of events)

"Non-naïve" patients are defined as patients who confirm (or whose legal representatives on behalf of the patient confirm) they have used, or are unable to confirm or deny if they have used, any prohibited medication within the past 42 days[3].

Provided the treating physician believes the patient will comply with the pre-treatment washout and complete the study protocol, the "non-naïve" patient will be given the opportunity to undergo a minimum of 42 days washout before returning for Baseline 1. Provided the patient (or their legal representatives on behalf of the patient) consent, the initial screening visit will be treated and confirmed as **Visit 0** (Figure 3-2).

**Visit 0** will commence study the run-in period where patients undergo a washout from prohibited medications. Patients are eligible to return for Baseline 1 after a minimum of 42 days washout. For patients (or their legal representatives on behalf of the patient) who confirm they have not used any prohibited medications for a minimum of 42 days, the second visit will be treated as **Visit 1 (Baseline 1)[4].**

A urine sample will be taken at **Visit 1** to assess the level of N-Acetyl-D-Leucine. Provided the level of N-Acetyl-D-Leucine is below the permitted threshold, the second visit will be confirmed as **Visit 1** (Baseline 1). **Visit 2** (Baseline 2/ Start of treatment period) will take place 14 days (+7 days) after **Visit 1.**

[2] If the treating physician has reason to believe the patient will not comply with the study run-in washout or the complete study protocol, the patient will be notified they are ineligible for the study.

[3] As described, "non-naïve" patients can also be defined as patients who were initially classified as "naïve," but whose initial urine sample unexpectedly detected levels of N-Acetyl-D-Leucine above the permitted threshold. Provided they are eligible, patients will be reclassified as "non-naïve" and return for a second screening visit after a minimum of 42 days washout.

[4] At Visit 1, patients who confirm (or whose legal representatives confirm) they have used, or are unable to confirm or deny if they have used, any prohibited medication within the past 42 days are ineligible to continue in the study.

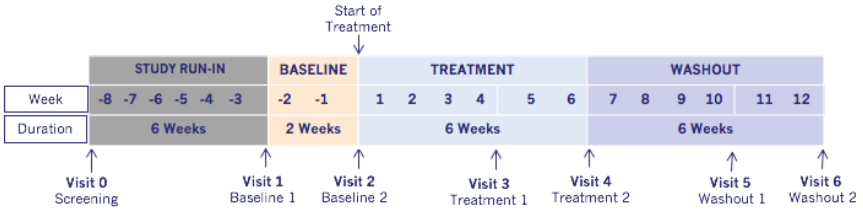


**Figure 3-2: Study Schema for Non-naïve Patients**

#### 3.1.2.2 Treatment Period

From **Visit 2** onward, all visits will be the same for all patients regardless of whether they were considered to be "naïve" or "non-naïve" at the time of screening.

During the treatment period, all patients will receive N-Acetyl-L-Leucine for 42 days (+7 days). **Visit 3** (Treatment 1) will occur at Day 28 (+7 days) of the treatment period and **Visit 4** (Treatment 2) will occur after the full 42 days (+7 days) of treatment.

#### 3.1.2.3 Washout Period

A 42-day (+7 days) washout period will be performed following treatment with N-Acetyl-L-Leucine. **Visit 5** (Washout 1) will occur on Day 28 (+7 days) of the washout period and **Visit 6** (Washout 2) will occur after the full 42 days (+7 days) of washout.

#### 3.1.2.4 Extension Phase

Patients who have participated in the study will be offered the opportunity to participate in a planned Extension Phase if the safety and tolerability during the 42-day (+7 days) treatment are considered to be acceptable by the Investigator for each specific patient, and the Investigator determines further treatment with IB1001 to be in the patient's interest. Provided the patient (or their legal representative on their behalf) subsequently consent to participate, the Extension Phase is planned to allow patients to have further access to IB1001 for one year.

Following a 6-week post Extension Phase treatment washout (Visit 10 of the Extension Phase), patients will have access to IB1001 for an additional one-year in the Extension Phase Treatment Period II.

**See Appendix 6 for the Protocol for Extension Phase.**

#### 3.1.2.5 COVID-19 Modifications to the Original Study Schema

COVID-19 has significantly impacted study subjects' ability to attend study visits due to government-ordered lockdowns or the closure of state (domestic) and/or national borders. In addition, the issuance of site-specific policies limiting or halting the conduct of non-essential study visits, the conversion of study-sites into COVID-19 wards, and site staff not on duty or reassigned to other priorities at the hospitals have affected the feasibility of conducting study visits. Finally, considering NPC patients are already classified as a vulnerable patient population, patients may be self-isolating.

If, per the reasons above, in-person visits cannot be carried out in accordance with the schedule of events, the following departures from the original study schema are allowed:

3.1.2.5.1 Non-Essential In-Person Visits: Treatment Visit 3/ Washout Visit 5

- Visit 3 and Visit 5 are “interim” visits of the treatment and washout phases, respectively.
- The Sponsor’s Medical Expert, Medical Monitor, the DSMB, Biostatistician and Principal Investigators consider that missing the in-person Visit 3 and / or Visit 5 would not compromise the safety of the patient or the integrity of the study, and that the patient could continue with medication (Visit 3) or the post-treatment washout phase (Visit 5) without attending the in-person Visit 3 and / or Visit 5. This risk assessment was based on the previously established safety profile of IB1001 (see Section 1), the observed very good tolerability shown to date in this ongoing, open-label study, including that no related serious adverse reactions had been reported with IB1001 (in any ongoing trial ), that these visits are not critical to the primary outcome assessment, and that the integrity of the clinical trial could be maintained if these visits were not performed due to COVID-19 restrictions.
- Therefore, in-person Visit 3 and Visit 5 have been classified as non-essential visits and may be skipped if they are not feasible to conduct in-person due to national, local, or site-specific restrictions, or necessary to safeguard the site staff, patients, and their families. If the in-person Visit 3 and / or Visit 5 is skipped, a remote visit should be conducted in lieu of the in-person visit (see Section 3.1.2.5.3 below).

3.1.2.5.2 Essential In-Person Visits: End of Treatment Visit 4/ Washout Visit 6

- Visit 4 and Visit 6 are the final visits of the treatment/washout phase (respectively)
- The Sponsor’s Medical Expert, Medical Monitor, the DSMB, and each Principal Investigator determined that the in-person Visit 4 and Visit 6 are necessary visits needed to fully assess the safety of trial participants, the primary endpoint, and maintain the integrity of the clinical trial.
- However, it was determined (if they are not feasible to conduct in-person due to national, local, or site-specific restrictions, or necessary to safeguard the site staff, patients, and their families) postponing the in-person Visit 4 and/or Visit 6 would not compromise the safety of the patient, and that the patient could continue with medication / be dosed longer than the planned 42 days (+7 days) treatment period (Visit 4). This risk assessment was based on the previously established safety profile of IB1001 (see Section 1), the observed good tolerability shown to date in this ongoing, open-label study, including that no related serious adverse reactions had been reported with IB1001 (in any ongoing clinical trial), that the Extension Phase (including one-year treatment period with IB1001) had been approved in all countries, and that data collected from these postponed in-person Visit 4 and/or Visit 6 was acceptable for the purpose of assessing a true treatment-related effect.
- Therefore, Visit 4 and Visit 6 have been classified as essential study visits which may be postponed (if they are not feasible to conduct in-person due to national, local, or site-specific restrictions, or necessary to safeguard the site staff, patients, and their families) but cannot be skipped. If Visit 4 and / or Visit 6 is postponed, a remote visit should be conducted at the time of the original the in-person visit (see Section 3.1.2.5.3 below)

3.1.2.5.3 Remote Visits

For any (i) skipped in-person Visit 3/5; (ii) postponed in-person Visit 4/6: based on the availability of the patient/ the study team, within approximately +/- 3 days of the originally

scheduled visit, the study team/ principal investigator (PI) should contact the patient (and as applicable, their parents/caregiver/legal representative) via phone/Skype[5] to collect information in order to monitor adverse or serious adverse events, and provide study oversight (hereafter referred to as "**remote visits")**.

Assessments which may be able to be performed remotely (as feasible) may include:

- Documentation of (changes in) frequency of therapy (hours per week)
- Documentation of (changes in) concomitant medication
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S)
- Clinical Global Impression of Change (CGI-C)
- Documentation of changes in or new adverse events / serious adverse events
- Discuss if additional study drug is needed (V3 only)
- PATA Speech Test
- Modified Disability Rating Scale
- Scale for the Assessment and Rating of Ataxia
- Additional Protocol Assessments which the Investigator/ Patient mutually agree to perform/assess

Assessments collected at a remote Visits 3 and/or Visit 5 should be entered into the electronic case report form (eCRF) under Visit 3 and/or Visit 5.

Assessments collected from remote Visit 4 and/or Visit 6 should be entered into eCRF as an Unscheduled Visit. When the postponed, in-person Visit 4 and/or Visit 6 is performed, all assessments collected at this visit should be entered into the eCRF as Visit 4 and/or Visit 6.

See Section 9.5 for additional information on how contingency measures/protocol deviations related to COVID-19 will be captured in the electronic case report form (eCRF)/ documented in the Parent Study Clinical Study Report (CSR).

#### 3.1.2.6 Interim Analyses

No interim analyses are planned throughout the Parent Study.

At the end of the Parent Study (defined as the date of the last visit of the last patient in the Parent Study globally; see Section 3.3) an interim clinical study report will be written which will include the results of the Parent Study.

### *3.1.3 Target Number of Patients*

- To be enrolled: Approximately 39 patients
- To be analyzed according to the modified Intention to Treat (mITT) analysis: Approximately 36 patients
- To be analyzed according to the Per Protocol Analysis: Approximately 30 patients

[5] As feasible; Skype is used as a generic term for videoconferencing, telemedicine but other software's may be used. No video recordings should be made of these remote visits.

#### *3.1.4 Number of Centers*

The trial will be conducted in a total of approximately 9 centers in the United States, the United Kingdom, Germany, Slovakia, or Spain, which must meet the structural and personnel requirements for performing the planned regular trial-related investigations.

If necessary, additional countries may be included in the trial.

#### *3.1.5 Study Duration*

The treatment and washout duration for all patients, from the first day of dosing with the study drug **(Visit 2)** to the final follow-up visit after washout (**Visit 6**), is expected to be approximately 84 days.

For "naïve" patients, there is a 14-day (+7 days) baseline period between **Visit 1** and **Visit 2.**

For "non-naïve" patients, there is a 42-day (+7 days) run-in period before **Visit 1,** and a 14-day (+7 days) baseline period between **Visit 1** and **Visit 2.**

COVID-19 will impact the duration of the study for patients whose Visit 4 and/or Visit 6 are postponed.

### 3.2 Discussion of Study Design

#### *3.2.1 Study Design*

[redacted]

[redacted]

**Two Study Schemas during Baseline Period**

As NPC is has an ultra-small patient population, and the number of eligible patients is already restricted, the study will permit patients who have used prohibited medications over the past 42 days to enroll provided they meet the inclusion/exclusion criteria and agree to perform a minimum 42-day washout from the prohibited medication prior to **Visit 1**.

### *3.2.2 Development of the Primary Endpoint: Clinical Impression of Change in Severity (CI-CS)*

The development of the CI-CS follows the recommendation of the US FDA and was designed in accordance with the FDA PRO Guidance and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force papers [ISPOR, 2018] to assist in establishing a well-defined and reliable blinded-clinician reported outcome assessment for use in the planned clinical studies [United States Department of Health and Human Services, 2018a].

The conceptual framework and description of the CI-CS methodology is provided in Fields, 2020.

#### *3.2.2.1 Anchor Tests: 9-hole Peg Test Dominant Hand (9HPT-D) or 8-meter Walk Test (8MWT)*

To account for the clinical heterogeneity of NPC and to better ensure that the primary assessment is clinically meaningful for each individual patient, the proposed CI-CS asks the treating physician to select, based on the patient's unique clinical symptoms, either the 9HPT-D or the 8MWT as an anchor test for the CI-CS. This decision will be made based on the treating physician's assessment of the patient at **Visit 1** (Baseline 1), before the start of treatment with N-Acetyl-L-Leucine. At the recommendation of the US FDA, a cognitive assessment should be performed at **Visit 1** according to the standard procedures of the clinical site to assist with the selection of the anchoring functional test appropriate for each patient from both a cognitive and a motor perspective [United States Department of Health and Human Services, 2018a]. The anchor test will also be selected based on interactions with the patient, their family, and caregivers, to ensure the selected scale is considerate of their quality of life.

As recommended by the US FDA, the 9HPT-D and 8MWT were selected as the anchor tests based on concept elicitation interviews with NPC clinical experts and representatives of NPC patient organizations worldwide [United States Department of Health and Human Services,

2018a], as well as questionnaire completed by parents caring for a child with NPC and NPC clinical experts [Cortina-Borja et al, 2018].

Based on these findings, it is proposed that physicians will be able to select either the 9HPT-D or the 8MWT as the anchor by which the CI-CS is assessed. The United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA, 2018], the Dutch Medicines Evaluation Board [MEB, 2018], and the Spanish Agency of Medicines and Medical Devices [AEMPS, 2018] all considered the 9HPT and 8MWT to be relevant, acceptable measures.

The US FDA initially suggested the 6-Minute Walk Test be used in lieu of the 8MWT. This was discussed extensively with the agency, who confirmed in the meeting notes that IntraBio provided additional rationale for the 8MWT over the 6-Minute Walk Test [United States Department of Health and Human Services, 2018a], including the consideration that from a clinical perspective, the 6-minute walk test is a crude measure of gait functionality, as the distance a patient can walk in 6 minutes does not equate to how stable their gait is or how secure their movement is. Although readily measurable, the 6-minute walk test is predominately a measure of strength and endurance, and therefore an appropriate for muscular dystrophy disorders but not muscular atrophy disorders [[redacted]].

Moreover, as discussed by representatives of the patient community and parents of patients with NPC and Tay-Sachs disease, the 6-minute walk test is described as being a poor measurement that is not clinically meaningful for patients or their families, as their interest is for patients' (many of whom are severely impaired) ability to perform acts of everyday life safely and securely rather than more exhaustive tasks [[redacted]].

*3.2.2.2 Blinded Raters & Video Assessments*

[redacted], having the primary evaluation of the CI-CS performed by two blinded, independent raters based on videos of the anchor test is intended to reduce detection and performance bias.

This decision was based on MHRA recommendation, which suggested and strongly endorsed the plan for blinded evaluation of video recordings of both the 9HPT-D and 8MWT [MHRA, 2018].

Based on the US FDA recommendation, the assessments and recordings will be made in the clinic rather than in the patient's home to standardize assessments across the diversity of patients' home environments [United States Department of Health and Human Services, 2018a].

In addition to adding blinded control to the primary assessment, at the recommendation of the US FDA, videos will be used to increase reliability and minimize testing burden on patients. Video recordings allow repeated viewings without the necessity for repetition and patient fatigue, and permit the blinded rater to control the pace of the movement analysis [Lord et al, 1998]. Finally, at the recommendation of the US FDA, basing the primary assessment on videos minimizes the recall bias that can be associated with the traditional Clinical Global Impression of Change (CGI-C) scale [United States Department of Health and Human Services, 2018a]. Each site will have the same video-recording devices and receive the same standardized training and instructions to create homogeneity in the video recordings.

The CI-CS will also be performed for the anchor test (9HPT-D or 8MWT) that was not selected as the patient's primary anchor test (i.e., the non-primary anchor test). This will enable the evaluation of both of the possible anchor tests, and to assess the appropriateness of the chosen primary anchor test with regard to its ability to function as a clinically meaningful outcome measure for the patient.

The blinded raters will be independent senior raters, who have ideally performed the 9HPT, 8MWT, and Clinical Global Impression (CGI) in a clinical setting. At the recommendation of the US FDA, definitions of disease severity and components for blinded raters to assess and rate the patients' change in severity will be provided [United States Department of Health and Human Services, 2018a]. The blinded raters will receive the same standardized training and instructions to create homogeneity in the assessments of patient's clinical change in severity while performing the 9HPT-D/8MWT.

#### *3.2.2.3 Serial Endpoint Evaluation*

Three additional visits have been added to the study so that patients will be assessed twice during each period (baseline, treatment, washout) based on the US FDA recommendation to have more frequent primary endpoint evaluations given the high degree of variability within these patient populations and in small sample sizes generally. These additional visits are intended to allow serial endpoint evaluations to mitigate against within-patient heterogeneity and missing data [United States Department of Health and Human Services, 2018a].

### *3.2.3 Choice of the Secondary and Exploratory Endpoints*

The proposed secondary endpoints for ataxia, described in Section 8.5.2, were selected on the recommendation of the US FDA to narrow the selection of secondary endpoints to minimize testing burden [United States Department of Health and Human Services, 2018a].

Ultimately, it was decided not to include the Niemann-Pick type C Clinical Severity Scale (NPC-CSS) or a modified version of NPC-CSS as a secondary endpoint for the Phase II Parent Study investigating the efficacy of 6-weeks of treatment with N-Acetyl-L-Leucine. This is because the NPC-CSS was designed to be a measure to characterize and quantify disease progression and is not a sensitive measure of short-term symptomatic treatment [Yanjanin et al, 2010]. The major domains of the NPC-CSS scale are each a 5-point scale recording the trajectory between normal functionality and negligible function. For a short-term study of 42 days (+7 days), the assessments are too crude to detect clinically meaningful effects.

Therefore, for the Phase II Parent Study, the NPC-CSS is too burdensome an endpoint, considering its graduation of changes is not fine enough to detect minor but clinically relevant changes in functioning / benefit after 42 days (+7 days) of treatment. However, a single NPC-CSS assessment will be performed at baseline Visit 1 to generate an additional measurement of disease severity at the start of the Parent Study.

Similarly, although IntraBio has demonstrated in *in vitro* studies that treatment with N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine corrects a number of phenotypes, including expanded lysosomal volume and the accumulation of sphingosines and glycosphingolipids in fibroblasts from patients with NPC and expanded lysosomal volume in NPC1-null CHO (Chinese hamster ovary) cells [Mann, 2018], for a short-term study of 6 weeks, no major changes in lysosomal volume/accumulation of sphingosines and glycosphingolipids can be expected to be detected by analyzing biomarkers.

### *3.2.4 Separate Trial Protocols by Indication*

[redacted]

[redacted]

## 3.3 End of Study Definition

A patient is considered to have completed the Parent Study if he/she has completed all phases of the Parent Study including the last visit (**Visit 6**).

The end of the Parent Study is defined as the date of the last visit of the last patient in the Parent Study globally. At this time, an interim report will be written which will include the results of the Parent Study.

A complete Clinical Study Report (CSR) will be written when the last visit of the last patient in the Extension Phase has been completed (see Section 3.3 of the Extension Phase in Appendix 6).

# 4 STUDY POPULATION

The study population comprises patients with NPC. To be eligible, patients must satisfy the following entry criteria:

## 4.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible to participate in the study:

1. Written informed consent signed by the patient and/or their legal representative/ parent/ impartial witness
2. Male or female aged ≥6 years in Europe OR ≥18 years in the United States with a confirmed diagnosis of NPC at the time of signing informed consent. Confirmed diagnosis includes [Patterson et al, 2017]:
   a) Clinical features and positive biomarker screen and/or filipin test without genetic tests results (has not been performed)
   b) Clinical features and positive genetic test
   c) Clinical features and positive biomarker screen and/or filipin test but only one NPC mutation identified on genetic test
   d) Clinical features with positive biomarker screen and/or filipin test and positive genetic test
3. Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, will be included if they are either sexually inactive (sexually abstinent[6] for 14 days prior to the first dose and confirm to continue through 28 days after the last dose) or using one of the following highly effective contraceptives (i.e. results in <1% failure rate when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:
   a) intrauterine device (IUD);
   b) surgical sterilization of the partner (vasectomy for 6 months minimum);
   c) combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal);
   d) progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable);
   e) intrauterine hormone releasing system (IUS);
   f) bilateral tubal occlusion.
4. Females of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

[6] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this trial abstinence is only acceptable if in line with the patient's preferred and usual lifestyle.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. As well, female condom and male condom should not be used together.

a) hysteroscopic sterilization;

b) bilateral tubal ligation or bilateral salpingectomy;

c) hysterectomy;

d) bilateral oophorectomy;

**OR** be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status. FSH analysis for postmenopausal women will be done at screening. FSH levels should be in the postmenopausal range as determined by the central laboratory.

5. Non-vasectomized male patient agrees to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study medication and the female partner agrees to comply with inclusion criteria 3 or 4. For a vasectomized male who has had his vasectomy 6 months or more prior to study start, it is required that they use a condom during sexual intercourse. A male who has been vasectomized less than 6 months prior to study start must follow the same restrictions as a non-vasectomized male.
6. If male, patient agrees not to donate sperm from the first dose until 90 days after their last dose.
7. Patients must fall within:
   a) A SARA score of $5 \leq X \leq 33$ points (out of 40)

   **AND**

   b) Either:
      i. Within the 2-7 range (0-8 range) of the Gait subtest of the SARA scale

      **OR**

      ii. Be able to perform the 9-Hole Peg Test with Dominant Hand (9HPT-D) (SCAFI subtest) in $20 \leq X \leq 150$ seconds.
8. Weight ≥15 kg at screening.
9. Patients are willing to disclose their existing medications/therapies for (the symptoms) of NPC, including those on the prohibited medication list. Non-prohibited medications/therapies (e.g. miglustat, concomitant speech therapy, and physiotherapy) are permitted provided:
   a) The Investigator does not believe the medication/therapy will interfere with the study protocol/results
   b) Patients have been on a stable dose/duration and type of therapy for at least 42 days before **Visit 1** (Baseline 1)
   c) Patients are willing to maintain a stable dose/do not change their therapy throughout the duration of the study.

10. An understanding of the implications of study participation, provided in the written patient information and informed consent by patients or their legal representative/parent, and demonstrates a willingness to comply with instructions and attend required study visits (for children this criterion will also be assessed in parents or appointed guardians).

### 4.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study:

1. Asymptomatic patients
2. Patient has clinical features of NPC and a positive biomarker screen and/or filipin test, but a completely negative result on a previous genetic test for NPC
3. Patients who have any of the following:
    a) Chronic diarrhea;
    b) Unexplained visual loss;
    c) Malignancies;
    d) Insulin-dependent diabetes mellitus.
    e) Known history of hypersensitivity to the Acetyl-Leucine (DL-, L-, D-) or derivatives.
    f) History of known hypersensitivity to excipients of Ora-Blend® (namely sucrose, sorbitol, cellulose, carboxymethylcellulose, xanthan gum, carrageenan, dimethicone, methylparaben, and potassium sorbate).
4. Simultaneous participation in another clinical study or participation in any clinical study involving administration of an investigational medicinal product (IMP; 'study drug') within 6 weeks prior to **Visit 1**.
5. Patients with a physical or psychiatric condition which, at the investigator's discretion, may put the patient at risk, may confound the study results, or may interfere with the patient's participation in the clinical study.
6. Known clinically-significant (at the discretion of the investigator) laboratories in hematology, coagulation, clinical chemistry, or urinalysis, including, but not limited to:
    a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5x upper limit of normal (ULN);
    b. Total bilirubin >1.5x ULN, unless Gilbert's syndrome is present in which case total bilirubin >2x ULN.
7. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.
8. Current or planned pregnancy or women who are breastfeeding.
9. Patients with severe vision or hearing impairment (that is not corrected by glasses or hearing aids) that, at the investigator's discretion, interferes with their ability to perform study assessments.
10. Patients who have been diagnosed with arthritis or other musculoskeletal disorders affecting joints, muscles, ligaments, and/or nerves that by themselves affects patient's mobility and, at the investigator's discretion, interferes with their ability to perform study assessments.

11. Patients unwilling and/or not able to undergo a 42-day washout period from any of the following prohibited medication prior to **Visit 1** (Baseline 1) and remain without prohibited medication through **Visit 6.**
    a) Aminopyridines (including sustained-release form);
    b) N-Acetyl-DL-Leucine (e.g. Tanganil®);
    c) N-Acetyl-L-Leucine (prohibited if not provided as IMP);
    d) Riluzole;
    e) Gabapentin;
    f) Varenicline;
    g) Chlorzoxazone;
    h) Sulfasalazine;
    i) Rosuvastatin.

### 4.3 Patient Withdrawal

Patients may withdraw from the study at any time at their own request without stating the reason(s) for withdrawal. If a patient withdraws early from the study after start of treatment an early termination (ET) visit should be arranged, preferably 7-14 days after the last dose of study drug.

"Non-naïve" patients (including "naïve" patients reclassified as "non-naïve") will be withdrawn from the study if their urine sample from **Visit 1** (Baseline 1) detects levels of N-Acetyl-D-Leucine above the permitted threshold.

The treating physician may decide that a patient should be withdrawn from the study or from the study drug. Reasons for withdrawal from the study or the study drug may include, but are not limited to, the following:

- Development of any adverse event (AE), serious AE (SAE), laboratory abnormality, condition, intercurrent illness, injury, medical condition, or use of a medication that is likely to interfere with patient safety, the overall assessment, or the study procedures, such that continued participation in the study would not be in the best interest of the patient.
- Consent withdrawal.
- The patient becomes pregnant or plans to become pregnant.
- Significant patient noncompliance, defined as an unwillingness to complete the procedures defined in the schedule of events.
- Patient lost to follow-up (i.e., staff unable to contact patient after several attempts).
- Investigator, Medical Monitor, and/or Sponsor decision for any other reason not listed above that may invalidate the results of the study or jeopardizes the health and/or safety of a patient
- Complications related to pandemics such as COVID-19.

Patients who discontinue study drug prior to completing the full treatment period, should be asked to complete the remaining study visits as far as possible and complete safety assessments at a minimum. If unwilling to complete the remaining study visits, regardless of the reason for withdrawal, best efforts should be made to have the patient take part in early termination (ET) procedures, preferably 7-14 days weeks following the last dose of the study drug, unless the

patient is lost to follow-up or has withdrawn his/her consent to further study participation. Due to COVID-19, the ET visit may need to be postponed or conducted remotely, after discussion with the PI and the Sponsor.

The reason for withdrawal will be recorded in the electronic case report form (eCRF). Adverse event follow-up procedures will be required if the patient is withdrawn from the study as a result of an AE/SAE. Data collected before withdrawal will be evaluated for safety and efficacy (if possible).

If the Investigator, Sponsor, or Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the clinical study may be terminated after appropriate consultation between the involved parties. The clinical study may also be terminated at the Sponsor's discretion in absence of such a finding. The reasons will be explained should the situation arise.

Conditions that may warrant termination of the study include (but are not limited to):

- The discovery of an unexpected, relevant, or unacceptable risk to patients;
- Failure to enroll patients at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the study drug.

Recruitment will continue until approximately 30 patients complete dosing and **Visit 6** or approximately 39 patients are enrolled.

### 4.4 Patient Identification

All patients (also referred to as "subject") will be assigned a unique, seven-digit identification number at screening, the "patient number". The first 4 digits will refer to the site: the first 2 numbers refer to the country (e.g. 49 for Germany, 34 for Spain, etc.) and the second 2 digits refer to the site number (e.g. 01 for the first site in German, 02 for the second site in Germany, etc.) (Figure 4-1).

The next 3 digits will refer to the indication/patient: the first digit will refer to the study (1 for the NPC study). The final two digits refer to the patient number.

The site and patient digits will be separated by a dash, e.g. 4901-101, 4301-105.

This unique patient number will not be replaced by an enrollment number if the patient is eligible and will start treatment.

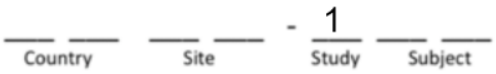


**Figure 4-1: Sample ID Format for a IB1001-201 Subject**

# 5 STUDY DRUG

## 5.1 Identity

**Product:** N-Acetyl-L-Leucine (internal development name: IB1001)

**Chemical name:** 2(S)-(acetylamino)-4-methylpentanoic acid

**Generic name:** N-Acetyl-L-Leucine

**Trade name:** to be determined

**Dosage form:** N-Acetyl-L-Leucine, 1000 mg powder for oral suspension in 60 mL glass bottles (without further excipients)

**Strength:** 1000 mg per 60 mL glass bottle

**Manufacturer:**

Manufacture of dosage form, QC testing, Stability studies:

[redacted]

Secondary packaging, Labelling, IMP release, Clinical distribution [7]

[redacted]

**Description:**

All patients are to receive N-Acetyl-L-Leucine (IB1001) in this single-arm study; there will be no comparator or placebo.

The product is formulated as 1000 mg powder for oral suspension, to be suspended in 40 mL Ora-Blend®.

The suspension vehicle Ora-Blend® contains the following excipients:

- purified water
- sucrose
- glycerin
- sorbitol
- flavoring
- microcrystalline cellulose
- carboxymethylcellulose sodium
- xanthan gum

**Commented [FP3]:** @Taylor: Ora-Blend at the moment is redacted in some sections of the protocol and not in others.
Is it the general fact that you use Ora-Blend as the suspension vehicle that you regard as commercially confidential? If so, then you would need to do a search for "Ora-Blend" in the document and redact everywhere.

Or is it just the details of the use (i.e. how many ml)? In this case it would be sufficient to just redact the respective information specifically.
E.g you would not need to redact the excipients, because once the reader knows that you are using Ora-Blend, the list of excipients is available in the public domain.

**Commented [TF4R3]:** got it, will not remove and will not remove the 1000 mg

[7] It is currently planned that in the event of Brexit without further (transitional) rules or in the event [redacted] is no longer able to carry out the importation and the final approval of the investigational drugs within the EU, [redacted] will assume responsibility for [redacted]

[redacted]

### 5.2 Administration

All patients are to receive N-Acetyl-L-Leucine (IB1001) in this single-arm study; there will be no comparator or placebo.

[redacted]

During the treatment period of this study, the dosing of the study drug is as follows:

- Patients aged ≥13 years in Europe and aged ≥18 years in the United States will take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing 15 to <25 kg will take 2 g per day: 1 g in the morning and 1 g in the evening.
- Patients aged 6-12 years weighing 25 to <35 kg will take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing ≥35 kg will take 4 g per day: 2 g in the morning, 1g in the afternoon and 1 g in the evening (as per patients aged ≥13).

The planned maximum dosage for patients ≥13 years, or aged 6-12 weighing ≥35 kg is 4 g per day for 42 days (+7 days).

Patients aged 6 to 12 years and <35 kg will receive 2 g or 3 g per day for 42 days (+7 days), in accordance with their body weight (see above).

### 5.3 Modification of Dose Schedule

On visit days, patients should keep to their usual dosing schedule.

If a patient misses a dose of study drug, the patient should wait and take the next dose according to the treatment schedule.

Compliance will be assessed upon a review of the inventory of IB1001 bottles returned from patients.

The patient's total daily dose may be reduced by up to one-half of their assigned dose at the discretion of the investigator.

In the event a patient turns 13 years old, or a patient aged 6-12 years old changes weight category over the course of the study, their daily dose will not change from the initial dosing regimen prescribed at Visit 2, the start of IMP.

Study drug will be taken during the 42-day (+7 day) treatment period. After the 42-day (+7 day) treatment period, patients will enter a 42-day (+7 day) washout period, which includes efficacy and safety assessments.

If Visit 4 is postponed due to COVID-19, patients who remain in the study must be dosed through the postponed Visit 4. The study drug will therefore be taken longer than the planned 42 days (+7 days). Based on the known risk/benefit profile of IB1001, the Sponsor's Medical Expert, Medical Monitor, the DSMB, and each Principal Investigator have determined that postponing Visit 4 will not compromise the safety of the patient, nor would continuing the patient on IMP until the postponed Visit 4.

*Note: at the time of the initial COVID-19 outbreak, the Extension Phase (providing patients with further access to treatment for one-year) had been accepted by all applicable Competent Authorities (CA)/ Institutional Review Boards (IRB)/ Research Ethics Committees (REC) where the trial is being conducted, supporting the continued dosing of patients until the postponed in person Visit 4.*

See Section 5.9 for information on the treatment of overdose.

### 5.4 Packaging, Labeling and Storage

[redacted]

Study drug will be packaged by [redacted] according to all local legal requirements. Study drug will be labelled in accordance with applicable regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

Packaging and labelling of IMP will comply with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) rules, Annex 13, and country-specific regulatory requirements. Packaging and labeling of the IMP will be available in the local language.

### 5.5 Blinding and Breaking the Blind

This study is not blinded.

### 5.6 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study. Study drug accountability will be performed at Visit 3 (only if feasible), Visit 4 (or after Visit 4, if IMP is returned via courier), and, if applicable, at the ET (or after ET, if the IMP is returned via courier). Unused or returned drug will be destroyed at the site. Alternatively, the study drug may be returned to [redacted]

[redacted] if sites are unable to dispose of the study drug and it cannot be destroyed at the site. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for maintaining up to date inventory and site accountability logs. Each dispensing of study drug to a patient will be documented in the medical records and patient-level accountability logs.

### 5.7 Investigational Medicinal Product (IMP; 'study drug') Compliance

Compliance will be assessed upon a review of the inventory of IB1001 bottles returned from patients.

Urine tests for N-Acetyl-D-Leucine will be done at **Visit 1, Visit 2** (baseline period), **Visits 5,** and **Visit 6** (washout period) (see Section 6.3.3 for more details).

If a patient initially classified as "naïve" has a urine sample after the initial screening visit which unexpectedly detects levels of N-Acetyl-D-Leucine above the permitted threshold, they will (provided eligible) be reclassified as "non-naïve". These patients are eligible to return for Visit 1 (Baseline 1) after a minimum 42-day wash-out.

"Non-naïve" patients (including "naïve" patients reclassified as "non-naïve") who test above the permitted threshold for N-Acetyl-D-Leucine in their urine at **Visit 1** (Baseline 1) will be classified as non-compliant and withdrawn from the study.

### 5.8 Concomitant Medications and Therapies

At **Visit 0/Visit 1**, all medication taken in the last 60 days prior to the date of informed consent must be recorded. The current amount (in hours per week) of therapy (e.g., physiotherapy, speech therapy) needs to be recorded at the time of informed consent.

Table 5.1 lists medications that are prohibited and must not have been used by the patient for at least 42 days before **Visit 1** (for both "naïve" and "non-naïve" patients). Medication not listed in this table may be permitted, at the discretion of the investigator, as long as there is no interference with the study objectives or patient safety. Doses of medications and therapies used for (the symptoms of) NPC should remain as constant as possible (at the investigator's discretion) throughout the trial.

**Table 5.1: Prohibited Medications**

| Prohibited medication | Washout prior to treatment (minimum time period) |
|---|---|
| Aminopyridines (including sustained-release form) | 42 days |
| N-Acetyl-DL-Leucine (e.g. Tanganil®) or N-Acetyl-L-Leucine (if not provided as study drug during the study) | 42 days |

[8] It is currently planned that in the event of Brexit without further (transitional) rules or in the [redacted] is no longer able to accept unused or returned study drug from European trial sites for destruction [redacted] will assume responsibility for [redacted]

**Table 5.1: Prohibited Medications**

| | |
|---|---|
| Riluzole | 42 days |
| Gabapentin | 42 days |
| Varenicline | 42 days |
| Chlorzoxazone | 42 days |
| Sulfasalazine | 42 days |
| Rosuvastatin | 42 days |

From **Visit 0 (non-naïve) or Visit 1** onward, any ongoing or new medication the patient takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

A patient who changes their previous regimen/dose, is permitted to continue with the study/study drug if the Investigator does not believe the medication/therapy will interfere with the patient's safety.

[redacted]

### 5.9 Treatment of Overdose

No specific information on overdose of N-Acetyl-L-Leucine (IB1001) exists for humans. Based on the pharmacology, it is not expected that overdose would produce a clinically relevant reaction. The patient should be appropriately monitored.

# 6 PARAMETERS AND METHODS OF ASSESSMENT

The primary and secondary parameters used during the study are described below.

Section 3 describes the Overall Design and Plan of Study for "naïve" and "non-naïve" patients. See Appendix 3A for "naïve" patients' schedule of events and Appendix 3B for "non-naïve" patients' schedule of events.

Section 7 contains more detailed information on which study assessments and procedures will be conducted for each study phase and visit.

## 6.1 Efficacy Parameters

### *6.1.1 Measurement of Clinical Impression of Change in Severity*

The primary endpoint is defined as the clinical impression of change in severity (CI-CS) comparing end of treatment with N-Acetyl-L-Leucine (Visit 4) with baseline (Visit 2) **minus** the CI-CS comparing the end of washout (Visit 6) with the end of treatment with N-Acetyl-L-Leucine (Visit 4) based on the primary anchor test.

This primary endpoint will assess the efficacy of N-Acetyl-L-Leucine for the treatment of NPC, based on blinded raters' CI-CS of patient's change in performance over 6 weeks on either the 9-hole peg test of the dominant hand (9HPT-D) or the 8-meter walk test (8MWT). A manual will be provided to each clinical site, which provides instructions for the administration of the CI-CS [Fields, 2020]. Similarly, a video-acquisition manual will be provided, which provides instructions for making standardized videos of the 8MWT and 9HPT-D anchor tests [redacted]

At Visit 1, the treating physician will evaluate each patient's clinical symptoms and select either the 9HPT-D or 8MWT as the primary anchor around which the CI-CS assessment will be based. The primary evaluation of the CI-CS will be performed by two independent raters whose assessments will be based on videos of the anchor test taken at each visit. The raters will be blinded to the treatment phases to reduce detection and performance biases and for each pair of visits will make an assessment based on a 7-point Likert scale, e.g., -3 = 'significantly worse', 0 = 'no change' to +3 = 'significantly improved' (see Section 8.5.1 for further details on the primary efficacy analysis).

#### 6.1.1.1 Secondary Efficacy Endpoints That Directly Supplement the Analysis of the Primary Endpoint

Supportive secondary endpoints will be evaluated that directly supplement the analysis of the primary endpoint as follows (see Section 8.5.2 for further details):

- The individual components of the primary endpoint, that is the CI-CS from Visit 2 to Visit 4 and the CI-CS from Visit 4 to Visit 6.
- Differences in the blinded rater's Clinical Impression of Severity (CI-S) values from baseline to end of treatment and from end of treatment to end of washout. The two CI-S values at each of these periods (Visit 1 and Visit 2 for baseline, Visit 3 and Visit 4 for end of treatment and Visit 5 and Visit 6 for end of washout) will be averaged.
- Sensitivity measurement of change in performance on either the 9HPT-D or the 8MWT on a 3-point scale. Using the CI-CS outcome for the primary anchor test based on the data for Visits 2 and Visit 4, any patient given a score of -1, -2, or -3 on the CI-CS will be classified as worsened (-1). Any patient classified as 0 on the CI-CS will be classified no change (0). Any patient given a score of +1, +2, +3 on the CI-CS will be classified as improved (+1). A similar classification will use the CI-CS comparing the end of

treatment with N-Acetyl-L-Leucine with end of washout based on the data for Visits 4 and Visit 6 and the difference between these scores calculated.
- An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test will also be undertaken. This will enable the separate analysis of CI-CS for both the 9HPT-D and the 8MWT.

There will also be an investigation of the intra-rater correlation in relation to Videos from Visits 1 and 2, Visits 3 and 4, and Visits 5 and 6 to help investigate the stability of the outcome evaluation and the disease itself. Pearson rank correlation coefficients will be calculated for each of these pairings for each of the two raters.

Other secondary endpoints include the Spinocerebellar Ataxia Functional Index (SCAFI) and Scale for Assessment and Rating of Ataxia (SARA) scores, based on the changes from baseline (Visit 2) to the end of treatment with N-Acetyl-L-Leucine (Visit 4), as well as from the end of treatment with N-Acetyl-L-Leucine (Visit 4) to the end of post-treatment washout (Visit 6). See Section 8.5.2 for further details on the analysis of the secondary efficacy endpoints.

### *6.1.2 Spinocerebellar Ataxia Functional Index (SCAFI)*

The SCAFI consists of a timed 8MWT to be carried out at maximum speed, the 9-hole peg test with both dominant and non-dominant hands (9HPT-D; 9HPT-ND) and the "PATA" test to measure speech performance. For the 8MWT and 9HPT tests, a lower score/time indicates a clinical improvement. A higher "PATA" test score indicates improvement in speech performance [Schmitz-Hübsch et al, 2008].

The SCAFI represents vital movement features (8MWT;9HPD-D/-ND for evaluation of the coordination of the upper extremities; PATA-test for evaluation of speech). After the assessment, raw scores are transformed into reciprocals and converted into subtest Z-scores. The final SCAFI is then generated as the arithmetic mean of all three Z-scores.

Two subtests, the 9HPT-D and 8MWT, will be videoed in a standardized format at every visit, except Visit 0.

A subset of the SCAFI, the 9HPT-D, serves as an inclusion criterion for the severity of ataxia at the beginning of the study prior to enrollment.

The complete SCAFI will be performed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

The score will be assessed by the investigator or qualified member of the study team.

6.1.2.1 Scale for the Assessment and Rating of Ataxia (SARA)

The SARA [Schmitz-Hübsch et al, 2006; Subramony, 2007] is an eight-item clinical rating scale (range 0–40, where 0 is the best neurological status and 40 the worst). It is a reliable and valid clinical scale with a high internal consistency that measures the severity of ataxia and increases with ataxia disease stage.

The SARA will serve as an inclusion criterion for the severity of ataxia at the beginning of the study.

The complete SARA will be performed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

The score will be assessed by the investigator or qualified member of the study team.

### *6.1.3 Measurement of Health-related Quality of Life*

The EuroQol (EQ)-5D-5L is a self-administered questionnaire for evaluating quality of life (QoL) introduced in 2009 [EuroQol Group, 2017].

The EQ-5D-5L is a multiple-choice questionnaire and a visual analogue scale that takes only few minutes to complete.

The EQ-5D-5L is a standardized measure of health status and in order to provide a simple, generic measure of health for clinical and economic appraisal and consists of 2 parts - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L will be used in patients aged ≥ 18.

The EQ-5D-Y is a child-friendly version of the EQ-5D, adapted to be appropriate for the measurement of health-related quality of life in young respondents [Wille et al, 2010]. It will be used in patients aged <18. If a patient turns 18 over the course of the Parent Study, they will continue to use the EQ-5D-Y for consistency.

The EQ-5D-5L/EQ-5D-Y will be assessed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

### *6.1.4 Measurement of Overall Neurological Status*

The modified disability rating scale (mDRS) will be used to evaluate the overall neurological status in NPC. The original scale developed in 2006 featured four assessment domains: ambulation, manipulation, language and swallowing [Iturriaga et al, 2006] and was further extended in 2010 to also include seizures and ocular movements [Pineda et al, 2010]. This scale can be used to evaluate the severity of disease, as well as monitor NPC progression, and the effect of treatment, both symptomatic and disease-specific.

The mDRS will be assessed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

### *6.1.5 Measurement of Global Impression*

The Clinical Global Impression (CGI) Scale has been long been implemented in neurodegenerative disease trials to provide an index of clinical importance that cannot be obtained from quantitative assessment measures [Quinn et al, 2008]. The CGI-C has been widely validated and used successfully across a range of conditions, including neurological disorders such as Alzheimer's disease [Schneider et al, 1997; Knopman et al, 1994], tardive dyskinesia [Solmi et al, 2018], and spinocerebellar ataxia [Monte et al, 2017], and other disorders such as radiologic findings in hypophosphatasia [Whyte et al, 2018]. It is currently being used in multiple clinical studies for NPC, including a Phase IIb/III clinical study of 2-hydroxypropyl-β-cyclodextrin (VTS-270; ClinicalTrials.gov ID: NCT02534844) and a Phase II/III clinical study of arimoclomol (NCT02612129).

The Clinical Global Impression of Severity (CGI-S) - physician asks the clinician one question:

> "Considering your total clinical experience with this particular population, how ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill the patient has been.

The CGI-S - caregiver asks the caregiver one question:

"Considering your total experience with this particular patient, how ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill the patient has been.

The CGI-S - patient asks the patient (*if able*) one question:

"Considering your total experience with this particular indication, how ill are you at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill I have ever been.

The CGI-S will be assessed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

The Clinical Global Impression of Change (CGI-C) - clinician asks the clinician one question:

"Compared to the patient's condition (i) Visit 2 (prior to medication) versus (ii) Visit 4 (end of medication) OR (i) Visit 4 (end of medication) versus (ii) Visit 6 (end of washout) OR (i) Early Termination Visit versus (ii) previous visit, this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment."

The Clinical Global Impression of Change (CGI-C) - caregiver asks the caregiver one question:

"Compared to the patient's condition (i) Visit 2 (prior to medication) versus (ii) Visit 4 (end of medication) OR (i) Visit 4 (end of medication) versus (ii) Visit 6 (end of washout) OR (i) Early Termination Visit versus (ii) previous visit, how much has he/she changed: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6=much worse; 7=very much worse since the initiation of treatment."

The Clinical Global Impression of Change (CGI-C) - patient asks the patient (*if able*) one question:

"Compared to how you were (i) Visit 2 (prior to medication) versus (ii) Visit 4 (end of medication) OR (i) Visit 4 (end of medication) versus (ii) Visit 6 (end of washout) OR (i) Early Termination Visit versus (ii) previous visit, how much have you changed: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6=much worse; 7=very much worse since the initiation of treatment."

The CGI-C – clinician/caregiver/patient will be assessed at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients).

### *6.1.6 NPC Clinical Severity Scale (NPC-CSS)*

The NPC clinical severity scale (NPC-CSS) [Yanjanin et al, 2010] was developed and validated in a cross-sectional study of current NPC patients and a longitudinal chart review of an historical cohort. The scale quantifies the major symptoms of NPC and characterizes the disease progression of NPC. The NPC-CSS measures clinical signs and symptoms in 9 major

(ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, swallowing) and 8 minor (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory problems) domains. A higher NPC-CSS score indicates a more severe clinical impairment and higher disease burden. An increase in the NPC-CSS score indicates a clinical worsening, while a decrease NPC-CSS score indicates a clinical improvement. A 0-point change in the NPC-CSS score represents a stabilization of disease progression, which is also a significant clinical improvement for rapidly progressive, neurogenerative diseases like NPC.

NPC-CSS is a widely accepted clinical outcome measure for NPC trials that investigate long-term treatment effect. Several clinical trials in patients with NPC have change in the NPC-CSS as primary endpoint, including a Phase IIb/III clinical trial of 2-hydroxypropyl-β-cyclodextrin (VTS-270; ClinicalTrials.gov ID: NCT02534844), a Phase II/III clinical trial of arimoclomol (NCT02612129), and an open-label Phase I/II clinical trial of lithium carbonate (NCT03201627). The ongoing Phase II/III trial of arimoclomol over 12 months has a modified version of the NPC-CSS as a primary endpoint, which includes 5 NPC-CSS domains: ambulation, speech, swallowing, cognition, and fine motor skills (EudraCT No. 2015-004438-93). These domains were identified by Cortina-Borja et al. (2018) as the most important manifestations of the disease for patients with NPC.

A recent consensus paper on clinical management guidelines for Niemann-Pick disease type C recommended that, bearing in mind the resources available to most physicians in practice, a modified version of the NPC-CSS that is widely used in clinical practice, and more user-friendly, should be administered. This modified version excludes the hearing and auditory brainstem response domains [Geberhiwot et al, 2018]. Accordingly, all major and minor domains of the NPC-CSS [Yanjanin et al, 2010] will be assessed in this study, with the exception of the hearing and auditory brainstem response domains. The change in the full NPC-CSS score, apart from hearing domains (i.e. hearing and auditory brainstem response), will be calculated.

In addition, the 5-domain version of the NPC-CSS (limited to the 5 major domains ambulation, cognition, fine motor, speech, and swallowing) which has been demonstrated to be a reliable surrogate for the complete NPC-CSS scale will be assessed [Cortina-Borja et al, 2018; Mengel et al, 2020].

The NPC-CSS / 5-Domain NPC-CSS is included as an exploratory endpoint in the Parent Study, as it may not sensitive enough to detect short-term changes in disease severity.

#### *6.1.7 Remote Assessments*

Due to COVID-19, safety and efficacy parameters may be collected remotely in lieu of in-person assessments (as feasible).

### 6.2 Safety Parameters

The Investigator is responsible for monitoring the safety of patients who have been enrolled in this study and for accurately documenting and reporting information as described in this section.
In addition, the investigator will monitor the degree of stress to patients and the risk threshold throughout the trial.

### *6.2.1 Adverse Events*

Patients will be instructed to report to the Investigator any AE that they experience. Investigators will ask about the occurrence of AEs at each visit. Investigators are required to document all AEs occurring during the clinical study, commencing with the signing of the informed consent form (ICF) through the End of Study Visit (scheduled at 42 days post last IB1001 dose). Adverse event recording will continue for patients who discontinue study treatment but remain on-study, until their ET Visit has been completed.

Adverse events will be recorded on designated eCRF pages. Each AE is to be characterized (i.e., verbatim term) and information provided regarding its seriousness, start and stop dates, intensity, outcome, and causal relationship with the study drug.

An AE is any undesirable physical, psychological or behavioral effect experienced by a patient during participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. This includes any untoward signs or symptoms experienced by the patient from the time of signing of the informed consent until completion of the study.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or medical staff
- Findings at physical examinations
- Laboratory abnormalities of clinical significance

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the investigational product are not considered AEs after treatment unless they reoccur after the patient has recovered from the preexisting condition or, in the opinion of the Investigator, they represent a clinically significant exacerbation in intensity or frequency. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the assessment returns to Baseline or until the Investigator determines that follow-up is no longer medically necessary.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event; Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as part of the subject's medical history.
- Pre-existing diseases or conditions present or detected prior to the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

It is important that Investigators record accurate AE terms on eCRFs. Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms will be identified by the Investigator and recorded on the eCRF. However, if an observed or reported

sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, or is atypical, it should be recorded as a separate AE on the eCRF.

#### *6.2.1.1 Adverse Event Intensity*

The Adverse Event Intensity refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

| | |
|---|---|
| **Mild:** | The AE does not interfere with the subject's routine activities. |
| **Moderate:** | The AE interferes with the subject's daily routine, but usual routine activities can still be carried out. |
| **Severe:** | The AE results in the inability to perform routine activities. |

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

#### *6.2.1.2 Adverse Event Relatedness*

The Principal Investigator (Investigator) will make a judgment regarding whether or not, in his/her opinion, the AE was related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE MUST be recorded on the adverse event eCRF. Below are guidelines for relationship assessment:

**Causality of Adverse Event:**

The Causality of Adverse Events refers to the relationship of the AE to study drug. Causality will be categorized according to the following criteria:

| | |
|---|---|
| **Not related:** | Adverse events for which a reasonable explanation for an alternative cause is considered plausible, e.g., no study drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship, or intercurrent illness. |
| **Related:** | Adverse events for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded, e.g., lacking plausible alternatives. |

### *6.2.2 Serious Adverse Events*

Serious adverse events will be reportable from the time the patient signs the ICF through their last study visit (e.g. Visit 6 or Visit 12) **or** until the Investigator in collaboration with IntraBio Ltd determines that follow-up is no longer necessary. Serious adverse events that are suspected to be drug related will be reported even if they occur up to 30 days after the patient has taken the last dose of study drug. If a related SAE is ongoing at the end of the study or when a patient

withdraws from the study, appropriate safety follow-up, including additional laboratory tests as required, will continue for 30 days.

An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or Birth Defect
- Important medical events that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

**Life-threatening experience**. Any adverse experience that places the patient, in the view of the reporter, at immediate risk of death from the adverse experience as it occurred, i.e., does not include an adverse experience that had it occurred in a more severe form, might have caused death.

**Required or prolonged inpatient hospitalization**. The adverse experience resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

**Persistent or significant disability/incapacity**. An adverse experience that resulted in a substantial disruption of a person's ability to conduct normal life functions.

**Congenital Anomaly.** The exposure of the patient to the drug or biologic during pregnancy that is judged to have resulted in the congenital anomaly/birth defect.

**Important medical events**. Adverse experiences that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Important medical events or interventions may be considered an SAE based upon medical judgment of the Investigator.

*6.2.2.1* ***Reporting Serious Adverse Events***

SAEs will be reported promptly once the Investigator determines that the event meets the protocol definition of an SAE. The Investigator or designate will fill out the SAE reporting form in the eCRF **within 24 hours of his/her becoming aware of these events**. In addition, for fatal and life-threatening events, the Sponsor's Medical Monitor should be contacted immediately. Contact numbers for the Medical Monitor (including after-hours cover) will be provided to the site before any patients are screened and upon receipt should be kept in the Site's study binder.

The SAE Reporting Form of the eCRF will always be completed as thoroughly as possible with all available details of the event within the designated time frames. The Investigator will always

provide an assessment of causality at the time of the initial report as described in Section 6.2.1.2.

If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before completing the form. The SAE reporting form will be updated when additional information is received **within 24 hours of receipt of such information**.

The completion of the SAE Reporting Form in the eCRF is the preferred method for Reporting SAEs. Only if a technical failure prevents the ability to report an SAE in the eCRF, then the paper SAE Reporting Form provided by the Sponsor must be completed and [redacted]

The fax and or email instructions can be found on the paper SAE Reporting Forms, which are filed in the Investigator Site File.

#### *6.2.2.2 Responsibilities of the Sponsor*

The Sponsor or their delegate, is responsible for fulfilling all obligations regarding notification of Regulatory Authorities, Independent Ethics Committees (IECs)/ Institutional Review Board (IRBs), and investigators according to applicable regulatory requirements (expedited and periodic reporting, e.g., serious unexpected suspected adverse reactions, Development Safety Update Report).

### *6.2.3 Pregnancy*

Every effort should be made to prevent pregnancy during the study treatment period. All patients of reproductive potential involved in the study are required to use highly effective methods of contraception during the study and for 28 days after the last IB1001 dose. Female patients will be instructed to notify the Investigator immediately if they discover they are pregnant. Pregnancy data during the study will be reported using the SAE reporting process (see Section 6.2.2). Since it will be necessary to collect detailed information on the course of any pregnancy occurring in a patient on study the Investigator will be provided with the pregnancy notification forms and specific guidance for completing these forms once the initial AE form documenting a pregnancy is received within 24 hours.

Pregnant patients will discontinue study medication for the duration of the pregnancy. The pregnancy will be followed by the Investigator and the outcome of the pregnancy will be reported to the Pharmacovigilance group.

At **Visit 2**, **Visit 4**, **Visit 6**, and then **Early Termination Visit** (if applicable**)**, females of childbearing potential will have a urine dipstick pregnancy test (analyzed on site).

### *6.2.4 Vital Signs*

Vital signs will be measured and recorded at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients). The following measurements must be performed: systolic/diastolic blood pressure and pulse. Vital signs will be measured after the subject has been in the supine position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the Investigator and must be reported on the corresponding eCRF.

Due to COVID-19, vital signs may not be able to be collected at the designated timepoints in the schedule of events (e.g. if visits are skipped and replaced by a remote visit or postponed). The Sponsor's Medical Expert, Medical Monitor, and DSMB deem the risk posed by vital

signs not being collected at the designated timepoints due to COVID-19 is acceptable in the context of remote visits where study staff will enquire regarding the health and wellbeing of the patient and assess for adverse events. This decision was based on the nature of the drug, the available non-clinical and clinical data for N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine (see Section 1), and the safety profile observed in this ongoing, open-label study (very well-tolerated) (and also in other ongoing trials with IB1001) to date.

#### *6.2.5 Electrocardiograms (ECGs)*

During the study, 12-lead ECGs will be performed approximately at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients). In addition, ECGs may be performed at other visits at the discretion of the Investigator if the findings from a previous ECG was clinically relevant.

The patient must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the patient is unable to be in the supine position, the patient should be in the most recumbent position possible.

All ECGs should be performed in a standardized method prior to blood draws or other invasive procedures.

Each ECG must include the following measurements:

Corrected QT, and whether the ECG is Normal, Abnormal NCS (not clinically significant), or Abnormal CS (clinically significant) for the patient.

The Principal Investigator or designated site physician will review and sign all ECGs. Results must be summarized in writing and classified as normal; Abnormal NCS (not clinically significant), or Abnormal CS (clinically significant) for the patient. Intervals of the ECG will be recorded in the eCRF. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

Due to COVID-19, ECGs may not be able to be collected at the designated timepoints in the schedule of events (e.g. if visits are skipped and replaced by remote visits or postponed) or if qualified study team members/ appropriate equipment are not available/accessible. The Sponsor's Medical Expert, Medical Monitor, and DSMB deem the risk posed by ECGs not being collected at the designated timepoints is acceptable in the context of remote visits where study staff will enquire regarding the health and wellbeing of the patient and assess for adverse events. This decision was based on the nature of the drug, the available non-clinical and clinical data for N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine (see Section 1), and the safety profile (no reports of cardiac issues, including QTc prolongation) observed in this ongoing, open-label study (and also in other ongoing trials with IB1001) to date. ECGs will be routinely collected at Visit 9 in the Extension Phase, allowing for further assessment of any cardiac effects.

#### *6.2.6 Physical Examinations*

Height and weight will be measured at the initial screening visit, **Visit 1** ("naïve" patients) or **Visit 0** ("non-naïve" patients).

#### *6.2.7 Additional Safety Assessments*

Not applicable.

## 6.3 *Laboratory* Parameters

### *6.3.1 Safety Laboratory Assessments*

The tests listed in Table 6.1 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients). Tests that are not done must be reported as such on the eCRFs.

Due to COVID-19, Safety Laboratory Assessments may not be collected at the designated timepoints in the schedule of events (e.g. if visits are skipped, performed remotely or postponed). The Sponsor's Medical Expert, Medical Monitor, and DSMB deem that the risk posed by safety laboratory assessments not being collected at the designated timepoints due to COVID-19 is acceptable in the context of remote visits where study staff will enquire regarding the health and wellbeing of the patient and assess for adverse events. This decision was based on to the nature of the drug, the available non-clinical and clinical data for N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine (see Section 1), and the safety profile observed in this ongoing, open-label study (and also in other ongoing IB1001 trials to date).

The total amount of blood taken per subject during the Parent Study will be approximately 66 mL (42 mL blood for the safety analyses, 24 mL blood for the PK analyses).

In the US, the safety laboratory assessments will be performed by [redacted] Laboratory sampling and processing will be defined by [redacted] standard procedures.

In Europe, the safety laboratory assessments will be performed by [redacted] Laboratory sampling and processing will be defined by [redacted] standard procedures.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting Investigator will use the clinical term rather than the laboratory term (e.g., anemia versus low hemoglobin value).

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**Blood Draw: Hematology**

- Hemoglobin
- Erythrocytes
- Hematocrit
- Thrombocytes
- Leukocytes

**Blood Draw: Clinical Chemistry**

- Sodium
- Lactate dehydrogenase (LDH)
- Potassium
- Creatinine
- Serum bilirubin level
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Urea

- Alkaline phosphatase (ALP)
- Follicle-stimulating hormone (FSH; for postmenopausal women only)

**Urine Safety Laboratories**

- Leukocytes
- Nitrite
- Urobilinogen
- Protein
- pH
- Occult blood (erythrocytes, leucocytes)
- Specific gravity
- Ketones
- Bilirubin
- Glucose

As described in Section 6.2.3 females of childbearing potential will have a urine dipstick pregnancy test analyzed on site at **Visit 2**, **Visit 4**, **Visit 6**, and the **Early Termination Visit** (if applicable**)**.

### *6.3.2 Measurement of N-Acetyl-L-Leucine Concentration in Blood*

Blood samples for measurements of N-Acetyl-L-Leucine concentrations will be taken at the time points designated on the schedule of events (Appendix 3A for "naïve" patients and Appendix 3B for "non-naïve" patients). Sparse PK sampling will be carried out at the same times that blood is drawn for the safety blood laboratory tests for possible future modeling purposes. This sampling is exploratory/descriptive.

For these PK analysis, Lithium-Heparin plasma samples will be drawn and frozen at -70ºC or below and shipped on dry ice for analysis at [redacted] Note, for each PK blood draw, it is important that the day and exact time of the last dose of N-Acetyl-L-Leucine before the blood draw and the day and exact time of the blood draw are recorded.

### *6.3.3 Measurement of N-Acetyl-D-Leucine Concentrations in Urine*

Urine samples will be collected for concentrations of N-Acetyl-D-Leucine at **Visit 1**, **Visit 2**, **Visit 5**, and **Visit 6**.

Urine samples for measurement of N-Acetyl-D-Leucine will be frozen at -70ºC or below and shipped on dry ice for analysis at [redacted]

The urine sample provided at **Visit 1** will be analyzed after it is received by [redacted] and results should be made available before start of the treatment phase to demonstrate that levels of N-Acetyl-D-Leucine are below the set threshold.

The urine samples provided at **Visit 2**, **Visit 5,** and **Visit 6** will be analyzed in batches and used for sensitivity analyses only.

### *6.3.4 Additional Laboratory Samples for Research Purposes*

Retained samples from the Parent Study may be used for research purposes to provide more information on the disease NPC.

### *6.3.5 Sample Processing*

IntraBio Ltd (or delegates) will provide a laboratory manual that will detail the logistics and handling of all samples taken during this study.

# 7 STUDY CONDUCT

Per Section 3.1.2.5, due to COVID-19, changes to existing study procedures have been/ may continue to be necessary in order to safeguard participants due to the outbreak of COVID-19 in the US and Europe, as well as their families and study teams.

## 7.1 Observations by Visit

At the initial screening visit, patients will be classified as "naïve" and "non-naïve" patients depending on their history and use of prohibited medications within the past 42 days. The schedule of events during the initial screening visit and throughout the baseline period (through **Visit 1**) will vary depending on patient's classification as "*naïve*" or "*non-naïve"*.

For all patients, **Visit 2 (Baseline 2)** should occur 14 days (+7 days) days after **Visit 1 (Baseline 1).**

**Visits 2** through **Visit 6** are the same for all patients and should occur within +7 days of the scheduled visit. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

### *7.1.1 Screening (Visit 0 or Visit 1)*

At the initial screening visit, after written informed consent has been obtained and while patients eligibility is being confirmed against the inclusion and exclusion criteria, patients (or their legal representative) will be asked to confirm whether the patient has used any of the prohibited medications within the past 42 days. This will determine whether the patient is classified as "naïve" or "non-naïve" and their respective baseline period before the treatment period.

Patients who confirm that they have not used any prohibited mediations within the past 42 days will be classified as "naïve" patients (Section 7.1.1.1).

Patients who confirm they have used, or are unable to confirm or deny if they have used, any prohibited medication within the past 42 days will be classified as "non-naïve" patients (Section 7.1.1.2).

*7.1.1.1 "Naïve" Patients Screening*

**Screening Visit/Visit 1** (Baseline 1)**:** Written informed consent will be obtained. All patients will be screened for inclusion and exclusion criteria. Only patients meeting all the inclusion and none of the exclusion criteria will be allocated to the trial. The Screening Visit will be treated as **Visit 1**: the first assessment of the baseline period. [9]

- Informed consent/informed consent form (ICF) signature and patient information
- Patient demographics[10]
- Patient weight and height measurements
- 60-day drug history including documentation of prior therapies/medications, including prohibited medications, concomitant medications/therapies for treatment of study-

[9] The Screening Visit will be confirmed as **Visit 1** as soon as the patient's eligibility is confirmed and the level of N-Acetyl-D-Leucine detected in their urine sample is confirmed to be below the permitted threshold. **Visit 1** will not be confirmed for patients classified as "naïve" but whose urine sample unexpectedly detect levels of N-Acetyl-D-Leucine above the permitted threshold. At the treating physician's discretion, these patients will be given the option to undergo a minimum of 42 days washout before returning for a second screening visit. Should they agree, the patient will be reclassified and changed to "non-naïve".

[10] Demographics for each patient will be collected in line with local regulations

specific illness, including frequency of therapy (e.g., physiotherapy, speech therapy) (documented in hours per week)
- Relevant medical history as well as medical history concerning the trial specific illness
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT) [11]
- Scale for Assessment and Rating of Ataxia (SARA)
- Check for remaining inclusion/exclusion criteria (including confirmation that prohibited medications have not been used for the past 42 days)
- Patient classified as "naïve"
- Vital signs
- Cognitive assessment according to standard procedures of the clinical site to assist with the Clinical Impression of Change in Severity (CI-CS) primary anchor test selection
- Determine Clinical Impression of Change in Severity (CI-CS) primary anchor test
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients <18 years old
- Modified Disability Rating Scale (mDRS)
- Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient (*if able)*
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests, including FSH for menopausal women (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

*7.1.1.2 "Non-naïve" Patients: Baseline Period*

**Screening Visit/Visit 0:** Written informed consent will be obtained. All patients will be screened for inclusion and exclusion criteria. Patients who confirm they have used or are unable to confirm or deny if they have used, any prohibited medications within the past 42 days will, at the treating physician's discretion, remain eligible for enrollment. The Screening Visit will be treated as **Visit 0.**

- Informed consent/informed consent form (ICF) signature and patient information
- Patient demographics
- Patient weight and height measurements
- 60-day drug history including documentation of prior therapies/medications, including prohibited medications, concomitant medications/therapies for treatment of trial-specific illness, including frequency of therapy (e.g., physiotherapy, speech therapy) (documented in hours per week)

[11] The 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videotaped in a standardized manner at every visit., except Visit 0. At Visit 1, these videos are made before the CI-CS primary anchor test is determined.

- Relevant medical history as well as medical history concerning the trial specific illness
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI)
- Scale for Assessment and Rating of Ataxia (SARA)
- Check remaining inclusion/exclusion criteria
- Patient classified as "non-naïve"
- Documentation of adverse events

**Visit 1** (Baseline 1)**:** Minimum of 42 days after **Visit 0**/washout from prohibited medication. All patients will be screened for inclusion and exclusion criteria. Only patients meeting the inclusion and none of the exclusion criteria will be allocated to the trial. This second visit will be treated as **Visit 1**: the first assessment of the baseline period. [12]

- Check of inclusion/exclusion criteria (including confirmation that prohibited medications have not been used within the past 42 days)
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording for Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT) [13]
- Scale for Assessment and Rating of Ataxia (SARA)
- Cognitive assessment according to standard procedures of the clinical site to assist with the Clinical Impression of Change in Severity (CI-CS) primary anchor test selection
- Determine Clinical Impression of Change in Severity (CI-CS) primary anchor test
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests, including FSH for menopausal women (done at central lab)
- Blood draw for sparse PK (done at PK Lab)
- Documentation of adverse events

[12] This screening visit will be confirmed as **Visit 1** provided the patient's eligibility is confirmed and the level of N-Acetyl-D-Leucine detected their urine sample is below the permitted threshold. Non-naïve patients whose urine sample after **Visit 1** unexpectedly detect levels of N-Acetyl-D-Leucine above the permitted threshold will be marked as non-compliant and withdrawn from the study.
[13] The 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videotaped in a standardized manner at every visit, except Visit 0. At Visit 1, these videos are made before the CI-CS primary anchor test is determined.

### *7.1.2 Baseline Visit (Visit 2)*

**Visit 2** (Baseline 2): Day 14 (+7 days) after **Visit 1** (Baseline 1). The final day/ second assessment of the baseline period. The start of the treatment period.

- Reconfirm patient eligibility, including confirmation that prohibited medications have not been used since **Visit 1**
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording for Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site before first dose of study drug is taken)
- Urine test for N-Acetyl-D-Leucine (test done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Dispensing of trial drug + intake of study drug at site

### *7.1.3 Treatment 1 (Visit 3)*

**Visit 3** (Treatment 1) Day 28 (+7 days) of treatment period: First assessment of treatment period with N-Acetyl-L-Leucine.

- Return of trial drug and compliance check (if feasible)
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead ECG
- Urinalysis (done at central lab)
- Blood draw for safety laboratory tests (done at central lab)

- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Dispensing of additional study drug *if needed*

### *7.1.4 Treatment 2 (Visit 4)*

**Visit 4 (**Treatment 2)**:** Day 42 (+7 days) of treatment period: the final day/second assessment of treatment period with N-Acetyl-L-Leucine. The start of washout period.

- Return of trial drug and compliance check[14]
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Visit 2** to **Visit 4**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Visit 2** to **Visit 4**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Visit 2** to **Visit 4**
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

### *7.1.5 Washout 1 (Visit 5)*

**Between Visit 4 – Visit 5: Wash-Out**

**Visit 5** (Washout 1)**:** Day 28 (+7 days) of wash-out period: First assessment of wash-out period.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)

[14] Or after Visit 4 if IMP is returned via courier

- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

### *7.1.6 Washout Visit 2 (Visit 6)*

**Visit 6** (Washout 2): Day 42 (+7 days) of washout period: the final day/second assessment of washout period.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Visit 4** to **Visit 6**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Visit 4** to **Visit 6**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Visit 4** to **Visit 6**
- Medication History: If the patient was classified as “naïve”, confirm if they have used N-Acetyl-Leucine (L, DL, D) at any time prior to Visit 1
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for laboratory safety tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Investigator determines continued treatment with IB1001 in patient’s best interest (if applicable)
- Informed consent/informed consent form (ICF) signature and patient information for Extension Phase (if applicable)
- Check of inclusion/exclusion criteria for Extension Phase (if applicable)

### *7.1.7 Early Termination Visit*

- Return of study drug and compliance check[15]
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Previous Visit** to **ET Visit**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Previous Visit** to **ET Visit**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Previous Visit** to **ET Visit**
- Medication History: If the patient was classified as "naïve", confirm if they have used N-Acetyl-Leucine (L, DL, D) at any time prior to Visit 1
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

[15] Or after ET if IMP is returned via courier

# 8 STATISTICAL METHODS

## 8.1 General Analysis Plan

### *8.1.1 Disposition of Patients*

The number of patients enrolled, plus the numbers contained within the Safety Analysis Set (SAF), the intention-to-treat analysis set (ITT), the modified intention-to-treat analysis set (mITT) and the Per Protocol Set (PPS) will be summarized overall and by country. The number of patients discontinuing treatment, together with the primary reason for discontinuation will be presented.

*Protocol Deviations*

Protocol deviations include but are not limited to:

- Violation of key inclusion/exclusion criteria
- Use of Prohibited Medications
- Inadequate study medication compliance
- Urgent/ contingency measures implemented due to COVID-19, including delayed or missed assessments due to postponed or skipped in-person visits

Further detail will be provided in the Statistical Analysis Plan (SAP)

### *8.1.2 Analysis Populations*

- The Safety Analysis Set (SAF) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine)
- The intention-to-treat analysis set (ITT) will consist of all patients in the SAF with a video recording at either Visit 1 or Visit 2 (or both)
- The modified intention-to-treat analysis set (mITT) will consist of all patients in the SAF with a video recording at either Visit 1 or Visit 2 (or both) and one video recording at either Visit 3 or Visit 4 (or both)
- The Per Protocol Set (PPS) will consist of all patients with video recordings at baseline (Visit 1 or Visit 2), end of treatment (Visit 3 or Visit 4), and end of washout (Visit 5 or Visit 6) and without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variable.

## 8.2 General Considerations

Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

All variables will be summarized using descriptive statistics. The number of patients, mean, standard deviation (SD), minimum, median, and maximum will be calculated for continuous and score variables. Frequency tables will be generated for categorical data.

A one-sided significance level of 5% will be used throughout for all endpoints as a guide for evidence for activity. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance with equal emphasis placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates.

No correction for multiple comparisons will be included.

## 8.3 Demographics, Baseline Characteristics and Concomitant Medications

Demographic data and patient characteristics at baseline will be summarized descriptively.

Frequency and percentage of prior and concomitant medication use will be summarized by World Health Organization (WHO) Drug dictionary coded terms - Anatomic Therapeutic Chemical (ATC) classification and preferred term.

### 8.4 Treatment Compliance

Summary statistics for the number of N-Acetyl-L-Leucine doses taken, based on bottles of Study Drug dispensed and return bottle counts, will be calculated for each visit. Overall compliance in terms of the percentage of drug taken based on these data will be summarized descriptively together with the proportion of patients who take at least 80% of the prescribed medication.

### 8.5 Efficacy Analyses

The primary analyses of efficacy will be based on the mITT. Analyses of efficacy based on the PPS will also be undertaken to provide supplementary information.

For each of the primary and secondary endpoints there will be separate analyses within key subgroups. The subgroups to be considered will be defined by:

- Naïve versus non-naïve as determined at screening
- Age (pediatric versus adult)
- Age/weight/dosing group
- Age of diagnosis: Early-infantile (<2 years), Late-infantile (2 to < 6 years), Juvenile (6 to < 15 years), Adolescent/Adult (≥ 15 years)
- Disease severity based on SARA below/ above the median SARA score at Visit 1
- Gender (male versus female)
- Region (US versus Europe)
- Primary Anchor Test (9HPT-D or 8MWT)
- Patients on miglustat versus patients not on miglustat
- Individual components of SARA scale: Gait Subtest
- Composite of SARA Subtests 1-4 (Gait, Stance, Sitting, Speech)
- Intra-patient variability between SARA score at Visit 1 (Baseline 1) versus Visit 2 (Baseline 2) (below/above median).
- Intra-patient variability between CI-S score Visit 1 (Baseline 1) versus Visit 2 (Baseline 2) (below/above median).

Additional subgroups can be added at the time of analysis on an exploratory basis.

Separate trials are planned to be conducted with N-Acetyl-L-Leucine for NPC, GM2-gangliosidosis, and ataxia-telangiectasia. There will however be a planned series of meta-analyses that will bring together the data from the studies for the primary and selected secondary endpoints. Further details will be provided in an MASAP.

#### *8.5.1 Primary Efficacy Endpoint*

The primary endpoint for the study is based on blinded raters' Clinical Impression of Change in Severity (CI-CS) comparing videos showing the patient's change in performance over 42 days (+7 days) on a pre-defined anchor clinical symptom scale: either the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or the 8 Meter Walk Test (8MWT). A manual will be provided to each clinical site, which provides instructions for the administration of the CI-CS [Fields,

2020]. Similarly, a video-acquisition manual will be provided, which provides instructions for making standardized videos of the 8MWT and 9HPT-D primary anchor tests [redacted]

The comparison of the Visit 4 video with the Visit 2 video and the comparison of the Visit 6 video with the Visit 4 video will provide the scores that contribute to the primary endpoint. Each of these comparisons will score change on a 7-point Likert scale (+3=significantly improved to -3= significantly worse).

During the pre-treatment period, the treating physician will evaluate each patient's clinical symptoms and select, at **Visit 1,** either the 9HPT-D or 8MWT as the primary anchor around which the CI-CS assessment will be scored. A cognitive assessment should be performed at **Visit 1** according to standard procedures of the clinical site to assist with the selection of the anchoring functional test appropriate for each patient from both a cognitive and a motor perspective.

The primary evaluation of the CI-CS will be performed by two independent raters whose assessments will be based on videos of the anchor test taken at each visit. These raters will be blinded to the treatment periods (baseline, treatment, or washout) to reduce detection and performance bias.

The primary endpoint is defined as the CI-CS comparing end of treatment with N-Acetyl-L-Leucine (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment with N-Acetyl-L-Leucine (Visit 4) based on the primary anchor test.

The CI-CS assessment will instruct the blinded rater to consider: *'compared to the first video, how has the severity of their performance on the 9HPT-D or 8MWT changed (improved or worsened) in 6-weeks as observed in the second video?'*

Each video pairing (CI-CS) will be read by the two independent raters, and the appropriate Likert scale score will be entered onto the eCRF. If there is a difference of one (1) point in the two primary blinded reviewers' CI-CS scores for a specific video pairing, the two scores will be averaged. If there is difference greater than one (1) point between the two primary blinded reviewers' CI-CS scores for a specific video pairing, an adjudication read will be triggered. In such cases, a third blinded reviewer will review the scores given from each of the two primary independent reviewers and determine which score is more accurate, that of reviewer A or reviewer B (adjudication by consensus). The adjudicator's decision will be the final score for that video assessment.

The statistical analysis of this endpoint will utilize a single sample t-test comparing the mean value of the primary endpoint with zero. This endpoint allows the effect N-Acetyl-L-Leucine to be measured both in terms of improvement during treatment followed by any deterioration once treatment is removed.

Summary statistics will in addition be calculated separately according to subgroups defined by the primary anchor test

### *8.5.2 Secondary Efficacy Endpoints*

A key Secondary Endpoint that will be evaluated to directly supplement the analysis of the primary endpoint is based on the independent raters' Clinical Impression of Severity (CI-S) of each video.

The independent raters will be given 6 videos of the patient's performance of the primary anchor test taken at Visit 1 to Visit 6. The videos will be labeled as Video A, B, C, D, E, F. The videos will be presented in a random order, and the independent raters will be blinded to the timepoint corresponding to each video.

For each video, the independent raters will make their evaluation of the CI-S, which asks: *"Considering your total clinical experience with this particular population, how ill is the patient at this time?"*

The CI-S is rated on a 7-point Likert scale ranging from + 3 (normal, not at all ill) to -3 (among the most extremely ill patients). For the CI-S, if there is one (1) point or more difference in the two blinded reviewers scores, the two scores will still be averaged.

Supportive secondary endpoints will be evaluated that directly supplement the analysis of the primary endpoint as follows:

- The CI-CS for end of treatment with N-Acetyl-L-Leucine (Visit 4) versus baseline (Visit 2) and end of washout (Visit 6) versus end of treatment with N-Acetyl-L-Leucine (Visit 4) will each be summarized descriptively.
- Improvement in the primary and non-primary anchor test measures will be evaluated based on the change in the blinded raters' Clinical Impression of Severity (CI-S) between baseline (average for Visit 1 and Visit 2) and end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) minus the change in CI-S between end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) and end of washout (average for Visit 5 and Visit 6). Statistical testing for the primary anchor test CI-S endpoint will be as for the primary endpoint. There will be no formal statistical testing of the non-primary test.
- Sensitivity measurement of change in performance on either the 9HPT-D or the 8MWT on a 3-point scale. Using the CI-CS outcome for the primary anchor test based on the data for **Visits 2** and **Visit 4,** any patient given a score of <0 on the CI-CS will be classified as worsened (-1). Any patient classified as 0 on the CI-CS will be classified no change (0). Any patient given a score of >0 on the CI-CS will be classified as improved (+1). A similar classification will use the CI-CS comparing the end of treatment with N-Acetyl-L-Leucine with end of washout based on the data for **Visits 4** and **Visit 6** and the difference between these scores calculated. The descriptive table will be similar to the primary endpoint. No statistical analysis will be performed.
- An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test (i.e., the non-primary anchor test) will also be undertaken. There will be no formal statistical testing of these endpoints, however.

Bland-Altman plots in relation to videos from Visits 1 and 2, Visits 3 and 4, and Visits 5 and 6 will be produced to help inform the stability of the outcome evaluation and the disease itself at baseline, end of treatment and end of washout. The scatter plot for videos from Visits 1 and 2 will place the average CI-S outcome of the videos from Visits 1 and 2 on the x-axis and the difference between those on the y-axis. A y=0 line will be placed on the plot for reference purposes. Similar plots will be produced for videos from Visits 3 and 4 and videos from Visits 5. and 6. Additional secondary endpoints will investigate other measures of symptoms and quality of life. Descriptive statistics will be provided for these measures at each visit and also changes from baseline (Visit 2) to the end of treatment with N-Acetyl-L-Leucine (Visit 4), as

well as end of treatment with N-Acetyl-L-Leucine (Visit 4) to the end of post-treatment washout (Visit 6) for the following measures:

- Spinocerebellar Ataxia Functional Index (SCAFI)[16]
- Scale for Assessment and Rating of Ataxia (SARA) score
- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[17] for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Treating Physician Clinical Global Impression of Severity (CGI-S) at every visit
- Treating Physician Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 4) to baseline (Visit 2), and end of washout (Visit 6) to end of treatment (Visit 4)
- Caregiver Clinical Global Impression of Severity (CGI-S) at every visit
- Caregiver Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 4) to baseline (Visit 2), and end of washout (Visit 6) to end of treatment (Visit 4)
- Patient Clinical Global Impression Scales Impression of Severity (CGI-S) at every visit *if they are able*
- Patient Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 4) to baseline (Visit 2), and end of washout (Visit 6) to end of treatment (Visit 4) *if they are able*

The SARA total score, the SCAFI total score, the individual SCAFI subtests: 9 Hole Peg Test with the Dominant Hand (9HPT-D), 8 Meter Walk Test (8MWT), and PATA test, will be evaluated statistically based on a single sample t-test or a single sample Wilcoxon Signed Rank test.

The individual SCAFI subtest: 9 Hole Peg Test with Nondominant hand (9HPT-ND), and the mDRS will be evaluated descriptively.

The CGI-S measures, and caregiver and patient CGI-C measures will be summarized descriptively. The CGI-C measures will be analyzed as for the CI-CS primary endpoint.

The measures of the two indices (-5L and -Y) of the EQ-5D descriptive system and measures of the two indices (-5L and -Y) of the EQ-5D visual analogue scale (VAS) will be evaluated descriptively.

### *8.5.3 Exploratory Efficacy Endpoints*

Sparse PK sampling will be collected to characterize the PK of N-Acetyl-L-Leucine in patients with NPC.

## 8.6 Missing Data

The primary endpoint will utilize assessments based on single video recordings at the end baseline period (**Visit 2**), end of the treatment period (**Visit 4**), and end of the washout period (**Visit 6**). If the **Visit 2** video is missing, the **Visit 1** video will be used in its place. Similarly, if the **Visit 4** and **Visit 6** videos are missing, **Visit 3** and **Visit 5** videos will respectively be used in their place.

[16]The 9 Hole Peg Test of the Dominant Hand (9HPT-D) and the 8 Meter Walk Test (8MWT), will be videoed for every patient at every visit except Visit 0
[17] European Sites Only

Analyses based on the mITT analysis set will utilize a last observation carried forward (LOCF) approach for missing videos from Visit 5 and Visit 6. For the primary endpoint CI-CS, this implies that the CI-CS value for **Visit** 4 to **Visit 6** will be assigned the value 0 (stable) if both videos from Visit 5 and Visit 6 are not available.

A sensitivity analysis will be undertaken to assess the robustness of the primary analysis of the primary endpoint which are based on LOCF in the mITT analysis set as follows:

If either video for Visit 3 or Visit 4 is available, but either video from Visit 5 and Visit 6 are unavailable, impute the value -1 (worsening) instead of 0 for the CI-CS for Visit 4 to Visit 6, unless the missingness is due to a "technical reason" (e.g. due to machine failure).

Additional methods to deal with missing data will be detailed in the SAP. Any changes from the SAP will be described and justified in the Clinical Study Report.

### 8.7 Blinding

The blinded independent raters will be given each of the 6 videos initially in a random order to make their evaluation of CI-S for each video. The blinded independent raters will then be provided with 3 pairs of video recordings blinded to information on the visits associated with these videos and their order and asked to provide a score for CI-CS for each pair. Further details regarding this blinding process will be detailed in the SAP.

### 8.8 Safety Analyses

The SAF will be the basis for all analyses of safety and tolerability.

### 8.9 Interim Analyses

There are no planned interim analyses.

### 8.10 Determination of Sample Size

It is postulated that N-Acetyl-L-Leucine will show effectiveness in 30% of patients and this success rate is viewed as being clinically important. Assuming that this group of patients will have scores that are evenly distributed across the values 1 and 2 for the primary endpoint and further that the remaining 70% of patients will have scores that are evenly distributed between the values -1, 0, and 1. The resulting mean score is 0.45 and the standard deviation (SD) for the primary endpoint under these assumptions is then 1.02. With 30 patients reporting on the primary endpoint, the study will have 76% power to detect a treatment benefit in a 5% one-sided one-sample t-test.

### 8.11 COVID-19 Details

This study is conducted during the COVID-19 outbreak. The following data capture decisions have been taken due to national, local, or site-specific restrictions imposed due to COVID-19, with the primary need to prioritize the safety of clinical study teams and patients, and to maintain the integrity of the study/data collection.

- All protocol deviations relating to COVID-19 are collected
- If in-person visits are not feasible, Visits 3 and / or 5 should be skipped and a remote visit conducted (i.e. phone, video conference)
- If in-person visits are not feasible, Visits 4 and / or 6 can be postponed until the in-person visit is feasible and should be performed in person.
- For skipped in-person Visit 3/5 or postponed in-person Visit 4/6, remote visits should occur approximately -/+ 3 days from the original visit (as feasible).

Currently, the complete impact of COVID-19 on the proposed statistical analyses is unknown. The statistical analysis plan already includes policies for handling missing data. Specific items/changes related to COVID-19 are being detailed in a separate document to the SAP (Addendum 1), which will be maintained throughout the study and adjusted as needed based on the duration and extent of the impact of the COVID-19 situation.

# 9 DATA HANDLING AND RECORD KEEPING

## 9.1 Data Collection

Study data for all patients will be collected in a confidential fashion using an electronic Case Report Form (eCRF). Access to the eCRF is restricted to staff members not involved in any aspect of the blinded evaluations. All the information required by the protocol must be documented and any omissions explained. The Investigator must review all eCRF entries for completeness and accuracy. Source documents, including all demographic and medical information, eCRFs and informed consent form for each patient in the study must be maintained by the Investigator. All information in the eCRFs must be traceable to the original source documents. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study. Concomitant medication and AEs will be coded using standardized medical dictionaries.

Responsible Monitor will review eCRFs entered by investigational staff for completeness and accuracy. Checks for data discrepancies in the eCRFs will be performed and the resulting queries will be notified to the investigational site. Designated Investigator site staff are required to respond to queries and make any necessary changes to the data.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined within a data handling plan/ data management plan.

## 9.2 Data Correction

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by the assigned Data Management Department and sent through the electronic data capture (EDC) system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved.

### *9.2.1 Deviations from the Protocol*

Deviations from the protocol will be judged during the study and/or when an individual patient's eCRF is completed (monitored) and documented in the protocol deviations log.

Protocol deviations will be classified (major/minor protocol deviations) for statistical analysis.

## 9.3 Data Quality Assurance

If applicable, the Sponsor (IntraBio Ltd.) and/or their representative (i.e. Monitor engaged by the Sponsor) will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

### *9.3.1 Retention of Records*

All essential documents must be safely retained by the Investigator for at least 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated; or if no application is filed or if the application is not approved for such indication for 15 years after the investigation is discontinued and the regulatory authorities are notified.

## 9.4 Protection of personal data

The completion of the Study involves the collection and processing of Personal Data. All processing of Personal Data at the clinic and by the Sponsor must be carried out in accordance with national legislation concerning the protection of Personal Data. Parties involved in the

process will observe the requirements provided under Regulation (EU) 2016/679 concerning general personal data protection.

The Investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The Investigator shall permit direct access to patients' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorized representatives of the Sponsor, Regulatory Authorities and IECs and IRBs.

As part of the required content of the informed consent, patients will be informed that their records may be reviewed by the Sponsor's designee and by regulatory agencies. Should access to medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

**9.5 COVID-19 Protocol Deviations and Missing Data**

Protocol deviations related to COVID-19 are documented. These deviations in protocol-specific procedures due to COVID-19 (changes in study visit schedules, remote and / or missed visits, or patient discontinuations) may lead to missing information.

For each patient, the eCRF will capture specific information that (as much as possible) explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information will be summarized in the Parent Study clinical study report.

# 10 QUALITY CONTROL AND QUALITY ASSURANCE

## 10.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at an investigators' meeting (if applicable), and during the Site Initiation Visit by the Sponsor and the monitor.

## 10.2 Training of Site Staff

The Principal Investigator (PI) is responsible for the conduct of the study at their study site, including delegation of specified study responsibilities and training of study staff. The PI shall ensure that the study is carried out in accordance with the protocol, ICH/GCP guidelines, and local regulations.
The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

## 10.3 Documentation and Filing

### *10.3.1 List of Patients (patient identification log)*

The Investigator will keep a confidential list of names of all patient participating in the study, so that the patients' records can be identified if necessary.

In addition, the Investigator will keep a list of all patients screened on a screening log to document identification of patients who were consented and entered study screening. If someone is not eligible to participate in the study, a reason must be provided.

### *10.3.2 Source Data*

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study). When a copy is used to replace an original document, the copy should fulfil the requirements for certified copies.

### *10.3.3 Investigator Site File / Regulatory Binder*

Before site initiation, an Investigator Site File (ISF) will be provided to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements that are required for study initiation at the investigational site.

From that point onwards, the Investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to the local regulatory requirements and agreement with the study Sponsor.

Details pertaining to the retention and archiving of study documents are found in Section 11.4.

### 10.4 Alternative Site due to COVID-19

Based on the exceptional circumstances of the COVID-19 pandemic and need to minimize risk (i.e. exposure to COVID-19) study visits may be conducted at alternative locations provided:

- The PI determines it is justified based on the personal benefit-risk ratio for the individual trial participant;
- The (i) patient and/or their family/ legal representative; (ii) PI / other applicable members of the study team; and, (iii) personnel at the alternative location (if applicable) consent to this alternative location
- Conducting the study visit at the alternative location does not pose an unacceptable safety risk (as agreed by (i) patient and/or their family/ legal representative; (ii)PI / other applicable members of the study team; and, (iii) personnel at the alternative location (if applicable)
- Traveling to/from this alternative location is permitted by national or local legislation and allowed by the alternative site and arrangements are made to provide adequate transportation (for applicable persons)
- If a study assessment cannot be performed at the alternative location, this should be documented and captured in the eCRF.

### 10.5 Monitoring

The monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the Investigator must grant direct access to the original patient's source documents.

The extent and nature of monitoring will be described in detail in the monitoring plan.

Due to COVID-19, alternative monitoring measures may be required if on-site monitoring is not permitted and deviations to the study monitoring schedule are necessary. If it is not possible to follow the IntraBio recommended monitoring schedule of onsite visits due to national, local, or site-specific restrictions, possible temporary, alternative measures may be implemented to maintain proper oversight of the clinical trials [IntraBio Ltd 2020b]. All monitoring deviations related to COVID-19 should be well-documented to enable appropriate evaluation of the clinical trials.

For all countries **except Slovakia:** Remote source data verification (SDV) will be allowed if it is permitted by the National Competent Authorities the site and Principal Investigator agree to this method of monitoring due to COVID-19 restrictions for onsite monitoring visits. To facilitate remote SDV, scans of source document worksheets, assessment forms, and other required documentation will be sent to the monitor. Monitors should be trained on remote SDV procedures. No protected health information should be scanned and sent to the monitors. If a site allows the monitors to have access to their electronic medical records, this should only be available to the monitor during the time of the remote visit. Site staff should be available to respond to monitors questions during the remote monitoring visit.

### 10.6 Audits and Inspections

The Sponsor's or designated vendor's Quality Assurance Department may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of the study. The Investigator is to notify the Sponsor immediately of any such inspection. The Investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities and will allow direct access to original source documents for monitoring, audits, and inspections.

# 11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

## 11.1 Good Clinical Practice

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance).

## 11.2 Informed Consent

A sample Informed consent form (ICF) will be provided to each site. No major deviations may be made from the sample ICF other than country- or region-specific formatting or requirements. The Sponsor and its advisors will review the draft ICF before it is finalized, and the final IRB/EC-approved documents must be provided to the Sponsor for regulatory purposes.

As required, approved IRB/EC patient facing documents like the ICF will be made available in the patients/ parent/ legal guardian's native language.

The ICF must be signed by the patient or the patient's legal guardian before his or her participation in the study. The Principal Investigator (PI) at each site will determine whether or not each patient has the capacity to give consent. When the patient is an adult (age 16 or older in the UK) and mentally impaired, and not able to give consent to confirm their willingness to participate in the study, a legal representative will be asked to decide on behalf of the patient if they will participate in the study.

The PI will determine a participant's capacity to consent according to the Mental Capacity Act (MCA). The PI will use a two-stage test of capacity to determine if a subject has the capacity to make a decision for themselves by considering:

- Does the patient have an impairment of the mind or brain (temporary or permanent), or is there some sort of disturbance affecting the way their mind or brain works?
- If so, does that impairment or disturbance mean that the patient is unable to make the decision in question at the time it needs to be made?

If the PI determines the patient is mentally able to understand the study and give their informed consent verbally, but the patient is not able to give the signature by him/herself because of physical impairment, the signature of an impartial witness will be accepted after the patient has given verbal informed consent.

The adult lacking capacity will also be informed as best as possible about the study according to, and at a level appropriate for, their capacity of understanding (as determined by the PI). No assent will be obtained from the impaired patient as standard, but the information discussed with the impaired adult patient will be documented in the patients records.

A copy of the ICF must be provided to the patient or the patient's legal guardian. If applicable, it will be provided in a certified translation of the local language. The original signed ICF must remain in each patient's study file and must be available for verification by study monitors at any time.

Due to COVID-19, reconsent for updated ICFs may be done remotely[18]. Approved updated patient information sheets and consent forms should be provided to trial participants by the investigator by e-mail, mail or courier before re-consent is obtained. The patient (or parent / legal representative) should be contacted by phone by the responsible site staff to discuss the updated ICF and answer all questions. After all questions have been answered and the patient (or parent/legal representative) has indicated their understanding of the ICF, oral consent should be obtained and documented. The patient (or parent/legal representative) will sign the ICF provided to them, and this will be returned to the site as soon as possible. A copy of the fully signed ICF will be provided to the patient (or parent/legal representative) as soon as possible.

Both parties should sign and date the ICF and the wet-ink signed ICF should be filed in the investigator site file. The exact procedures by which remote ICF was obtained should be recorded in the patient source documents and / or on the applicable ICFs forms

### 11.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local regulatory requirements. The Sponsor must ensure that all ethical and regulatory requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

In accordance with applicable regulatory body guidance's issued in relation to COVID-19, changes to the protocol may need to be implemented without REC/IRB approval or before filing an amendment to the CTA/IND to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) and to maintain the integrity of the clinical trial.

Any guidance issued by the Sponsor to clinical trial sites describing deviations in protocol-specific procedures which may be necessary due to COVID-19 should be submitted to the applicable CA/REA/IRB for reference at the time they are issued. All changes will be reported afterwards in a substantial amendment (SA) protocol application.

### 11.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 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 investigational product.

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[18] *Per EMA Guidance on the Management of Clinical Trials during the COVID-19 (CORONAVIRUS) Pandemic, Version 3, during the outbreak of COVID-19 "it should be avoided that trial participants visit trial sites for the sole purpose of obtaining re- consent."*

However, these documents should be retained for a longer period if required by the applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 11.5 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB), in conjunction with the study Medical Monitor and/or Sponsor, is responsible for the oversight of the safety. For this purpose, the DSMB will receive regular updates of safety.

The DSMB will review all safety data on a regular basis. The exact content of review material and the frequency of review will be detailed in the DSMB charter.

The DSMB will also be involved in risk-assessments of the impact of COVID-19, and reviewing any guidance issued by the Sponsor in regard to the global pandemic. They may give recommendations on the conduct of trial operations and protocol adjustments which may be required in light of COVID-19.

### 11.6 Premature Termination of the Study

If Sponsor, an Investigator, or regulatory authorities discover conditions during the study that indicate that the study or related activities at a particular site should be terminated, this action may be taken after appropriate consultation between Sponsor and the Investigator. Conditions that may warrant study or site termination include but are not limited to:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
2. Patient recruitment is unsatisfactory
3. Data recording is inaccurate or incomplete
4. Investigator(s) do not adhere to the protocol or applicable regulatory guidelines in conducting the study
5. GCP is not being maintained or adequately followed
6. Administrative reasons
7. Complications related to pandemics such as COVID-19
8. Reasons unrelated to the study.

Study or site termination and follow-up will be performed in compliance with the conditions set forth in 21 Code of Federal Regulations (CFR) Section 3.1.2 and/or other national and local regulations, as applicable, and in compliance with the principles set forth in International Conference on Harmonization (ICH) Good Clinical Practices (GCPs) and ethical principles established by the Declaration of Helsinki.

### 11.7 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to IntraBio or affiliates by their patient number allocated in the trial, not by name. Documents not to be submitted to IntraBio or affiliates that identify the patient (e.g., the signed informed consent, patient identification list) must be maintained by the Investigator as part of the ISF in a secure and confidential manner.

### 11.8 Liability and Insurance

In accordance with the relevant national regulations, the Sponsor will take out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

### 11.9 Publication Policy

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.

It is understood that the Clinical Trial is part of the Multi-Center Clinical Trial and publication of results is expected. IntraBio will actively pursue publication of the results of the study in cooperation with the Principal Investigators (PIs), subject to the terms and conditions of the clinical trial agreement between IntraBio, the Investigator, and their respective clinical trial site.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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# 13 APPENDICES

## 13.1 Appendix 1: Synopsis

| CLINICAL STUDY PROTOCOL SYNOPSIS | |
|---|---|
| **SPONSOR:** | IntraBio Ltd. [redacted] |
| **US LEGAL REPRESENTATIVE:** | IntraBio Inc [redacted] |
| **EU LEGAL REPRESENTATIVE:** | IntraBio Ireland Ltd [redacted] |
| **STUDY NUMBER:** | IB1001-201 |
| **EUDRACT NUMBER:** | 2018-004331-71 |
| **IND NUMBER:** | 134369 |
| **PRODUCT/COMPOUND:** | N-Acetyl-L-Leucine (IB1001) |
| **TITLE:** | Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C: A multinational, multicenter, open-label, rater-blinded Phase II study.<br><br>*Short Title: A safety and efficacy study of N-Acetyl-L-Leucine on Niemann-Pick type C.* |
| **CLINICAL PHASE:** | Phase II |
| **(TARGET) INDICATION(S):** | Niemann-Pick disease type C |
| **STUDY SITES:** | US and Europe |
| **VERSION & DATE:** | Version 7.0, 10-OCT-2022 |

**Confidentiality Statement**

This clinical study protocol is the confidential information of IntraBio Ltd. and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation and may not be used for any purpose without the prior written consent of IntraBio Ltd.

| | |
|---|---|
| **Name of Sponsor/Company:**<br>IntraBio Ltd. | |
| **Protocol Number:**<br>IB1001-201 | **Phase of Development:**<br>Phase II |
| **Title of the Protocol:**<br>Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C: A multinational, multicenter, open-label, rater-blinded Phase II study.<br><br>**Short title:**<br>*Short Title: A safety and efficacy study of N-Acetyl-L-Leucine on Niemann-Pick type C* | |
| **Purpose:**<br>The primary purpose of the study is to evaluate the safety and efficacy of N-Acetyl-L-Leucine (IB1001) in the treatment of Niemann-Pick disease type C (NPC) | |
| **Study Rationale:**<br>The goal of this study is to demonstrate that N-Acetyl-L-Leucine is efficacious in improving symptoms, functioning, and quality of life against the defined endpoints in patients with NPC for the purpose of establishing the benefit/risk balance of the investigational medicinal product in the proposed clinical setting.<br><br>N-Acetyl-L-Leucine is the L-enantiomer of N-Acetyl-DL-Leucine, a modified amino acid that has been available in France since 1957 under the trade name Tanganil® (Pierre Fabre Laboratories) as a treatment for acute vertigo and is available as a solution for injection and as a tablet. N-Acetyl-L-Leucine is not currently authorized anywhere in the world for the treatment of any condition.<br><br>The Sponsor's (IntraBio Ltd.) development of Acetyl-Leucine for NPC began with the investigation of the commercially available racemic mixture, N-Acetyl-DL-Leucine (Tanganil®). Published case studies are available in the literature describing the effect of acute treatment with the racemate N-Acetyl-DL-Leucine in patients with NPC disease [Bremova et al, 2015] as well as with Cerebellar Ataxias [Strupp et al, 2013; Schniepp et al., 2016]. An additional case series is available in the literature describing the disease modifying effect of long-term treatment with N-Acetyl-DL-Leucine [Cortina-Borja et al, 2018]. In all studies, the compound was well-tolerated with no discernible serious side effects.<br><br>These preliminary findings have been corroborated by *in vitro* studies with fibroblasts from NPC patients and by *in vivo* studies in the *Npc1*$^{-/-}$ model for NPC disease to explain the pharmacological properties of N-Acetyl-D-Leucine in relation to the observed therapeutic effects [Mann, 2018; Platt, 2018].<br><br>Recent *in vitro* and *in vivo* studies have demonstrated that the L-enantiomer is believed to mediate the therapeutic effect and have potential clinical benefits over the racemic mixture. IntraBio therefore intends to focus further development on N-Acetyl-L-Leucine without the presence of D- | |

enantiomer. The safety profiles of both N-Acetyl-DL-Leucine and N-Acetyl-L-Leucine have been characterized in both preclinical and clinical studies, and on the basis of compassionate use experience with N-Acetyl-DL-Leucine in NPC (as well as in patients with other lysosomal storage disorders, neurodegenerative and genetic diseases, and further indications) [Dr Michael Strupp, MD, Professor of Neurology LMU Munich, Personal Communication].

Based on these findings, IntraBio is conducting a Phase II study investigating the efficacy and safety of N-Acetyl-L-Leucine for the treatment of NPC. Patients will only be included in the study if they meet the inclusion and exclusion criteria described in the study protocol approved by the relevant ethics committees and the regulatory authorities and informed consent is obtained. To further minimize risks, patients will receive the best available clinical care to manage the underlying conditions with careful monitoring of adverse events that may arise during the course of the clinical study.

The confidentiality of all patients will be protected by pseudonymization and in accordance with guidelines and local laws.

**Primary Objective**:

The primary objective is to evaluate the efficacy of N-Acetyl-L-Leucine based on blinded raters' Clinical Impression of Change in Severity (CI-CS) in the treatment of NPC.

**Secondary Objectives:**

- To assess the clinical efficacy of N-Acetyl-L-Leucine on symptoms of ataxia, functioning, and quality of life for patients with NPC;
- To evaluate the safety and tolerability of N-Acetyl-L-Leucine at 4 g/day in adults and children with NPC, including patients aged ≥18 years in the United States and patients aged ≥13 years in Europe, and weight-tiered doses in children 6 to 12 years of age in Europe

**Exploratory Objectives:**

- To characterize the pharmacokinetics (PK) of N-Acetyl-L-Leucine in patients with NPC

**Primary Endpoint:**

The primary endpoint is defined as the Clinical Impression of Change in Severity (CI-CS) comparing end of treatment with N-Acetyl-L-Leucine (Visit 4) with baseline (Visit 2) **minus** the CI-CS comparing the end of washout (Visit 6) with the end of treatment with N-Acetyl-L-Leucine (Visit 4) based on the primary anchor test.

This primary endpoint will assess the efficacy of N-Acetyl-L-Leucine for the treatment of NPC, based on blinded raters' CI-CS of patient's change in performance over 6 weeks on either the 9-hole peg test of the dominant hand (9HPT-D) or the 8-meter walk test (8MWT).

At Visit 1, the treating physician will evaluate each patient's clinical symptoms and select either the 9HPT-D or 8MWT as the primary anchor around which the CI-CS assessment will be based. The primary evaluation of the CI-CS will be performed by two independent raters whose assessments will be based on videos of the anchor test taken at each visit. The raters will be blinded to the treatment phases to reduce detection and performance biases and for each pair of visits will make an assessment based on a 7-point Likert scale, e.g., -3 = 'significantly worse', 0 = 'no change' to +3 = 'significantly improved'.

**Secondary Endpoints:**

There will be several secondary endpoints that closely relate to the primary endpoint:

- The CI-CS for end of treatment with N-Acetyl-L-Leucine (Visit 4) versus baseline (Visit 2) and end of washout (Visit 6) versus end of treatment with N-Acetyl-L-Leucine (Visit 4) will each be summarized descriptively.
- Improvement in the primary and non-primary anchor test measures will be evaluated based on the change in the blinded raters' Clinical Impression of Severity (CI-S) between baseline (average for Visit 1 and Visit 2) and end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) minus the change in CI-S between end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) and end of washout (average for Visit 5 and Visit 6). Statistical testing for the primary anchor test CI-S endpoint will be as for the primary endpoint. There will be no formal statistical testing of the non-primary test.
- Sensitivity measurement of change in performance on either the 9HPT-D or the 8MWT on a 3-point scale. Using the CI-CS outcome for the primary anchor test based on the data for **Visits 2** and Visit **4,** any patient given a score of -1, -2, or -3 on the CI-CS will be classified as worsened (>0). Any patient classified as 0 on the CI-CS will be classified no change (0). Any patient given a score of +1, +2, +3 on the CI-CS will be classified as improved (>0). The descriptive table will be similar to the primary endpoint. No statistical analysis will be performed
- An evaluation of the CI-CS An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test (i.e., the non-primary anchor test) will also be undertaken. There will be no formal statistical testing of these endpoints, however.

The following assessments will be based on the absolute changes from baseline (**Visit 2**) to the end of treatment with N-Acetyl-L-Leucine (**Visit 4**), as well as end of treatment with N-Acetyl-L-Leucine (**Visit 4**) to the end of post-treatment washout (**Visit 6**)[19].

- Spinocerebellar Ataxia Functional Index (SCAFI)[20]
- Scale for Assessment and Rating of Ataxia (SARA) score
- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[21] for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Treating Physician Clinical Global Impression of Severity (CGI-S)
- Treating Physician Clinical Global Impression of Change (CGI-C) [22]
- Caregiver Clinical Global Impression of Severity (CGI-S)
- Caregiver Clinical Global Impression of Change (CGI-C)[4]
- Patient Clinical Global Impression of Severity (CGI-S) *if they are able*
- Patient Clinical Global Impression of Change (CGI-C)[4] *if they are able*

**Safety Parameters:**

Adverse events (AEs), safety laboratory tests including biochemistry, hematology, urinalysis including pregnancy test, vital signs, 12-lead electrocardiogram (ECG), and concomitant

[19] See the SAP for complete methods of dealing with missing data as well as how secondary endpoints will be investigated descriptively.
[20] Two subsets, the 9-hole peg test of the dominant hand (9HPT-D) and the 8-meter walk test (8MWT), will be videoed for every patient at every visit, except Visit 0.
[21] European Sites Only
[22] Based on the changes from baseline to the end of treatment with N-Acetyl-L-Leucine, as well as end of treatment with N-Acetyl-L-Leucine to the end of post-treatment washout. The two CI-S values at each of these periods (Visit 1 and Visit 2 for baseline, Visit 3 and Visit 4 for end of treatment and Visit 5 and Visit 6 for end of washout) will be averaged.

medications. Blood samples may be collected or retained for research purposes about the disease NPC.

*Note: in the Extension Phase, physical exams are also conducted.*

**Pharmacokinetics (PK):** Sparse PK sampling will be carried out at **Visits 1, 2, 3, 4, 5** and **6** (at the same times that blood is drawn for the safety blood laboratory tests) for possible future modeling purposes. This sampling is exploratory/descriptive.

Lithium-Heparin plasma samples will be drawn and frozen at -70ºC or below and shipped on dry ice for analysis at [redacted] Note, for each PK blood draw, it is important that the day and exact time of the last dose of N-Acetyl-L-Leucine before the blood draw and the day and exact time of the blood draw are recorded.

*Note: In the Extension Phase, full PK sampling will take place at baseline (Visit 7B) and after 1-year treatment (Visit 9B).*

Urine samples will also be collected for concentrations of N-Acetyl-D-Leucine at **Visit 1**, **Visit 2**, **Visit 5**, and **Visit 6**.

Urine samples for measurement of N-Acetyl-D-Leucine will be frozen at -70ºC or below and shipped on dry ice for analysis at [redacted]

The urine sample provided at **Visit 1** will be analyzed after it is received by [redacted] and results should be made available before start of the treatment phase to demonstrate that levels of N-Acetyl-D-Leucine are below the set threshold.

The urine samples provided at **Visit 2**, **Visit 5,** and **Visit 6** will be analyzed in batches and used for sensitivity analyses only.

**Study Design and Methodology:**

This is a multinational, multicenter, open-label, rater-blinded Phase II study. In the Parent Study, patients will be assessed during three study periods: a baseline period, treatment period, and a washout period.

As it is not uncommon for symptoms and functioning to fluctuate over a week, to help account for intra-patient variability, patients will be assessed twice during each period.

At the initial screening visit, patients will be classified as either "naïve" or "non-naïve" patients depending on their use of prohibited medications within the past 42 days. The schedule of events during the initial screening visit and throughout the baseline period (through **Visit 1**) will vary depending on patient's classification as either "naïve" or "non-naïve".

After **Visit 2**, all visits will be the same for all patients regardless of whether they were considered to be "naïve" or "non-naïve" at the time of enrollment.

**Screening/Baseline Period**

***Study Schema 1: "Naïve" Patients***

"Naïve" patients are defined as patients who, at the initial screening visit, confirm (or whose legal representatives confirm on behalf of the patient) that they have not used any prohibited medications within the past 42 days. For these patients, the initial screening visit will be treated as **Visit 1** (Baseline 1).

A urine sample will be taken at **Visit 1** to detect N-Acetyl-D-Leucine. Provided the patient's levels of N-Acetyl-D-Leucine are below the permitted threshold, the initial screening visit will be confirmed as **Visit 1** (Baseline 1). **Visit 2** (Baseline 2/Start of treatment period) will take place 14 days (+7 days) after **Visit 1** (Figure 1).

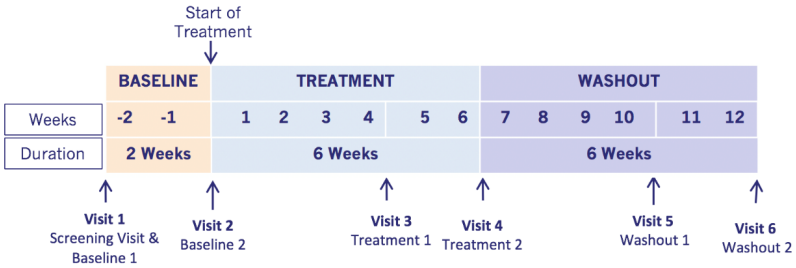


**Figure 1: Study Schema for "Naïve" Patients**

**Reclassifying "Naïve" Patients to "Non-naïve" Patients**

**Visit 1** will not be confirmed for "naïve" patients whose urine sample unexpectedly detected levels of N-Acetyl-D-Leucine above the permitted threshold. Provided the treating physician believes the patient will indeed comply with the pre-treatment washout and complete study the protocol[23], these patients will be given the option to undergo a minimum of 42 days washout before returning for a second screening visit. Provided the patient (or legal representative on behalf of the patient) consent, the patient will be reclassified as "non-naïve" and will return for a repeat Visit 1 after the study run-in washout period.

***Study Schema 2: "Non-naïve" Patients***

"Non-naïve" patients are defined as patients who confirm (or whose legal representatives on behalf of the patient confirm) they have used, or are unable to confirm or deny if they have used, any prohibited medication within the past 42 days[24].

Provided the treating physician believes the patient will comply with the pre-treatment washout and complete the study protocol, the "non-naïve" patient will be given the opportunity to undergo a minimum of 42 days washout before returning for a second screening visit. Provided the patient (or their legal representatives on behalf of the patient) consent, the initial screening visit will be treated and confirmed as **Visit 0** (Figure 2).

**Visit 0** will commence study run-in period where patients undergo a washout from prohibited medications. Patients are eligible to return for a second screening visit after a minimum of 42 days washout. For patients (or their legal representatives on behalf of the patient) who confirm they have not used any prohibited medications for a minimum of 42 days, the second screening visit will be treated as **Visit 1 (Baseline 1)[25].**

A urine sample will be taken at **Visit 1** to assess the level of N-Acetyl-D-Leucine. Provided the level of N-Acetyl-D-Leucine is below the permitted threshold, the second screening visit will be

[23] If the treating physician has reason to believe the patient will not comply with the pre-treatment washout or the complete study protocol, the patient will be notified they are ineligible for the study.

[24] As described, "non-naïve" patients can also be defined as patients who were initially classified as "naïve," but whose initial urine sample unexpectedly detected levels of N-Acetyl-D-Leucine above the permitted threshold. Provided they are eligible, patients will be reclassified as "non-naïve" and return for a second screening visit after a minimum of 42 days washout.

[25] At Visit 1, patients who confirm (or whose legal representatives confirm) they have used, or are unable to confirm or deny if they have used, any prohibited medication within the past 42 days are ineligible to continue in the study.

confirmed as **Visit 1** (Baseline 1). **Visit 2** (Baseline 2/ Start of treatment period) will take place 14 days (+7 days) after **Visit 1.**

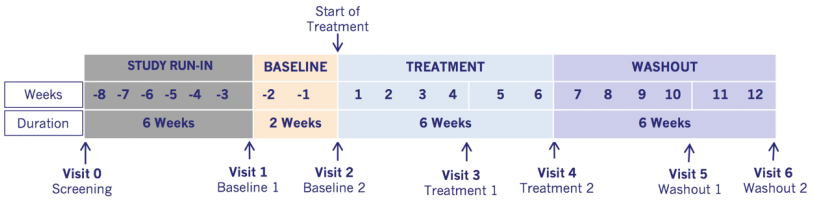


**Figure 2: Study Schema for Non-Naïve Patients**

**Treatment Period:**
During the treatment period, all patients will receive N-Acetyl-L-Leucine for 42 days (+7 days). **Visit 3** (Treatment 1) will occur at Day 28 (+7 days) of the treatment period and **Visit 4** (Treatment 2) will occur after the full 42 days (+7 days) of treatment.

**Washout Period:**
A 6-week washout period will be performed following treatment with N-Acetyl-L-Leucine. **Visit 5** (Washout 1) will occur on Day 28 (+7 days) of the washout period and **Visit 6** (Washout 2) will occur after the full 42 days (+7 days) of washout.

**Remote Visits:**
For any (i) skipped in-person Visit 3/5; (ii) postponed in person Visit 4/6: based on the availability of the patient/ the study team, within approximately +/- 3 days of the originally scheduled visit, the study team/ PI should contact the patient (and as applicable, their parents/caregiver/legal representative) via phone/Skype[26] to collect information in order to monitor adverse or serious adverse events, and provide study oversight (hereafter referred to as "**remote visits")**.

**Extension Phase**:
Patients who have participated in the study will be offered the opportunity to participate in a planned Extension Phase (EP) if the safety and tolerability during the 42 day (+7 day) treatment are considered to be acceptable by the Investigator for each specific patient, and the Investigator determines further treatment with IB1001 to be in the patient's interest. Provided the patient (or their legal representative on their behalf) subsequently consent to participate, the Extension Phase is planned to allow patients to have further access to IB1001 for two, one-year treatment periods (Extension Phase Treatment Period I, Visit 8 + Visit 9, and Extension Phase Treatment Period II, Visits 11 and 12). The two, one-year EP treatment periods are separated by a washout period of approximately 42 days (+14 days) (Visit 10).

[26] As feasible; Skype is used as a generic term for videoconferencing, telemedicine but other software's may be used. No video recordings should be made of these remote visits.

**COVID-19:**

This study is ongoing during the COVID-19 outbreak. Coronavirus (COVID-19) outbreaks have been recorded in all countries with study sites and subjects participating in IntraBio's clinical trials and have significantly impacted the IB1001-201clinical trial.

The global pandemic has had a significant impact on the IB1001-201 clinical trial by impacting study subjects' ability to attend study visits due to government-ordered lock downs, or the closure of state (domestic) and/or national borders. In addition, the issuance of site-specific policies limiting or halting the conduct of non-essential study visits, the conversion of study-sites into COVID-19 wards, and site staff not on duty or reassigned to other priorities at the hospitals have affected the feasibility of conducting study visits. Finally, considering NPC patients are already classified as a vulnerable patient population, patients may be self-isolating.

Therefore, protocol deviations and changes to study visits have been /may be necessary in order to safeguard participants, their families, and study teams. These include:

- Visit 3 and Visit 5 are "interim" visits of the treatment/washout phase (respectively), and the in-person visit may be skipped;
- Visit 4 and Visit 6 are final visits of the treatment/washout phases and the in-person visit may be postponed, but cannot be skipped;
- For any (i) skipped in-person Visit 3/5; (ii) postponed Visit 4/6: based on the availability of the patient/ the study team, within approximately +/- 3 days of the originally scheduled visit, a remote visit should be conducted;
- If a visit is skipped or postponed, protocol-specific procedures may not take place at the designated timepoint in the schedule of events.

**Schedule of Events:**

An outline of the Parent Study design, defined by Visit, and per study schema, is shown below. For a detailed description of the study design and the tests procedures and assessments performed at each visit, refer to the Schedule of Events in Appendix 3A for "naïve" patients and 3B for "non-naïve" patients.

**"NAÏVE" PATIENTS: SCREENING PERIOD**

**Screening Visit/Visit 1** (Baseline 1)**:** Written informed consent will be obtained. All patients will be screened for inclusion and exclusion criteria. Only patients meeting all the inclusion and none of the exclusion criteria will be allocated to the trial. The Screening Visit will be treated as **Visit 1**: the first assessment of the baseline period.[27]

- Informed consent/informed consent form (ICF) signature and patient information
- Patient demographics[28]
- Patient weight and height measurements
- 60-day drug history including documentation of prior therapies/medications, including prohibited medications, and concomitant medications/therapies for treatment of trial-specific illness

[27] The Screening Visit will be confirmed as **Visit 1** as soon as the patient's eligibility is confirmed and the level of N-Acetyl-D-Leucine detected in their urine sample is confirmed to be below the permitted threshold. **Visit 1** will not be confirmed for patients classified as "naïve" but whose urine sample unexpectedly detect levels of N-Acetyl-D-Leucine above the permitted threshold. At the treating physician's discretion, these patients will be given the option to undergo a minimum of 42 days washout before returning for a second screening visit. Should they agree, the patient will be reclassified and changed to "non-naïve".

[28] Demographics for each patient will be collected according to local laws

- Relevant medical history as well as medical history concerning the trial specific illness, including frequency of physiotherapy and speech therapy (documented in hours per week)
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT) [29]
- Scale for Assessment and Rating of Ataxia (SARA)
- Check for remaining inclusion/exclusion criteria (including confirmation that prohibited medications have not been used for the past 42 days)
- Patient classified as "naïve"
- Vital signs
- Cognitive assessment according to standard procedures of the clinical site to assist with the Clinical Impression of Change in Severity (CI-CS) Primary anchor test selection
- Determine Clinical Impression of Change in Severity (CI-CS) Primary anchor test
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients <18 years old
- Modified Disability Rating Scale (mDRS)
- Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient (*if able)*
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests, including follicle stimulating hormone (FSH) for menopausal women (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

**"NON-NAÏVE" PATIENTS: SCREENING PERIOD**

**Screening Visit/Visit 0:** Written informed consent will be obtained. All patients will be screened for inclusion and exclusion criteria. Patients who confirm (or whose legal representatives on behalf of the patient confirm) they have used, or are unable to confirm or deny if they have used, any prohibited medications within the past 42 days will, at the treating physician's discretion, remain eligible for enrollment. The Screening Visit will be treated as **Visit 0.**

- Informed consent/ ICF signature and patient information
- Patient demographics
- Patient weight and height measurements
- 60-day drug history including documentation of prior therapies/medications, including prohibited medications, and concomitant medications/therapies for treatment of trial-specific illness
- Relevant medical history as well as medical history concerning the trial specific illness, including frequency of physiotherapy and speech therapy (documented in hours per week)
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI)
- Scale for Assessment and Rating of Ataxia (SARA)
- Check remaining inclusion/exclusion criteria
- Patient classified as "non-naïve"
- Documentation of adverse events

[29] The 9-hole peg test of the dominant hand (9HPT-D) and 8-meter walk test (8MWT) will be videotaped in a standardized manner at every visit, except Visit 0. At Visit 1, these videos are made before the CI-CS primary anchor test is determined.

**Visit 1** (Baseline 1)**:** Minimum of 42 days after **Visit 0**/washout from prohibited medication. All patients will be screened for inclusion and exclusion criteria. Only patients meeting the inclusion and none of the exclusion criteria will be allocated to the trial. This second screening visit will be treated as **Visit 1**: the first assessment of the baseline period. [30]

- Check of inclusion/exclusion criteria (including confirmation that prohibited medications have not been used for the past 42 days)
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT) [31]
- Scale for Assessment and Rating of Ataxia (SARA)
- Cognitive assessment according to standard procedures of the clinical site to assist with the Clinical Impression of Change in Severity (CI-CS) primary anchor test selection
- Determine Clinical Impression of Change in Severity (CI-CS) primary anchor test
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Modified Disability Rating Scale (mDRS)
- Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead EC
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests, including FSH for menopausal women (done at central lab)
- Blood draw for sparse PK (done at PK Lab)
- Documentation of adverse events

**FOR ALL PATIENTS ("NAÏVE" AND "NON-NAÏVE")**

**Visit 2** (Baseline 2): Day 14 (+7 days) after **Visit 1** (Baseline 1). The final day/ second assessment of the baseline period. The start of the treatment period.

- Reconfirm patient eligibility**,** including confirmation that prohibited medications have not been used since Visit 1
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)

[30] This screening visit will be confirmed as **Visit 1** provided the patient's eligibility is confirmed and the level of N-Acetyl-D-Leucine detected their urine sample is below the permitted threshold. Non-naïve patients whose urine sample after **Visit 1** unexpectedly detect levels of N-Acetyl-D-Leucine above the permitted threshold will be marked as non-compliant and withdrawn from the study.
[31] The 9-hole peg test of the dominant hand (9HPT-D) and 8-meter walk test (8MWT) will be videotaped in a standardized manner at every visit, except Visit 0. At Visit 1, these videos are made before the CI-CS primary anchor test is determined.

- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site before first dose of study drug is taken)
- Urine test for N-Acetyl-D-Leucine (test done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Dispensing of trial drug + intake of study drug at site

**Visit 3** (Treatment 1) Day 28 (+7 days) of treatment period: First assessment of treatment period with N-Acetyl-L-Leucine

- Return of trial drug and compliance check (if feasible)
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead ECG
- Urinalysis (done at central lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Dispensing of study drug *if needed*

**Visit 4 (**Treatment 2)**:** Day 42 (+7 days) of treatment period: the final day/second assessment of treatment period with N-Acetyl-L-Leucine. The start of washout period.

- Return of trial drug and compliance check[32]
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver

[32] Or after Visit 4 if IMP is returned via courier

- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Visit 2** to **Visit 4**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Visit 2** to **Visit 4**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Visit 2** to **Visit 4**
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

**Between Visit 4 – Visit 5: Wash-Out**
**Visit 5** (Washout 1)**:** Day 28 (+7 days) of wash-out period: First assessment of wash-out period.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

**Visit 6** (Washout 2): Day 42 (+7 days) of washout period: the final day/second assessment of washout period.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Visit 4** to **Visit 6**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Visit 4** to **Visit 6**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Visit 4** to **Visit 6**
- Medication History: If the patient was classified as “naïve”, confirm if they have used N-Acetyl-Leucine (L, DL, D) at any time prior to Visit 1
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)

- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for laboratory safety tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events
- Investigator determines continued treatment with IB1001 in patient's best interest (if applicable)
- Informed consent/informed consent form (ICF) signature and patient information for Extension Phase (if applicable)
- Check of inclusion/exclusion criteria for Extension Phase (if applicable)

**Early Termination Visit**

- Return of study drug and compliance check[33]
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for adults aged ≥18 years, EQ-5D-Y for children aged <18 years
- Modified Disability Rating Scale (mDRS)
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on **Previous Visit to ET Visit**
- Clinical Global Impression of Change (CGI-C) by caregiver based on **Previous Visit to ET Visit**
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on **Previous Visit to ET Visit**
- Medication History: If the patient was classified as "naïve", confirm if they have used N-Acetyl-Leucine (L, DL, D) at any time prior to Visit 1
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for sparse PK (done at PK lab)
- Documentation of adverse events

**Number of Patients:**

- To be enrolled: Approximately 39 patients
- To be analyzed according to the modified Intention to Treat (mITT) analysis: Approximately 36 patients
- To be analyzed according to the Per Protocol Analysis: Approximately 30 patients

[33] Or after ET if IMP is returned via courier

**Number of Sites:**

Approximately 9 sites

**Number of Participating Countries:**

Approximately 9 sites in the United States, United Kingdom, Germany, Spain, and Slovakia

If necessary, additional countries may be included in the trial.

**Study Duration:**

The treatment and washout duration for the Parent Study for all patients, from the first day of dosing with the study drug **(Visit 2)** to the final follow-up visit after washout (**Visit 6**), is expected to be approximately 84 days.
For "naïve" patients, there is a 14-day (+7 days) screening/ baseline period between **Visit 1** and **Visit 2.**
For "non-naïve" patients, there is a 42-day (+7 days) run-in period before **Visit 1,** and a 14-day (+7 days) screening/ baseline period between **Visit 1** and **Visit 2.**

The total duration of the Parent Study may be impacted if Visit 4 and/or Visit 6 are postponed due to COVID-19.

**Study Population and Criteria for Inclusion/Exclusion:**

**Inclusion Criteria:**

Individuals who meet all of the following criteria are eligible to participate in the study.

1. Written informed consent signed by the patient and/or their legal representative/ parent/ impartial witness
2. Male or female aged ≥6 years in Europe OR ≥18 years in the United States with a confirmed diagnosis of NPC at the time of signing informed consent. Confirmed diagnosis includes [Patterson et al. 2017]:
   a) Clinical features and positive biomarker screen and/or filipin test without genetic tests results (has not been performed)
   b) Clinical features and positive genetic test
   c) Clinical features and positive biomarker screen and/or filipin test but only one NPC mutation identified on genetic test
   d) Clinical features with positive biomarker screen and/or filipin test and positive genetic test.
3. Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, will be included if they are either sexually inactive (sexually abstinent[34] for 14 days prior to the first dose and confirm to continue through 28 days after the last dose) or using one of the following highly effective contraceptives (i.e. results in <1% failure rate

[34] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this trial, abstinence is only acceptable if in line with the patient's preferred and usual lifestyle.
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. As well, female condom and male condom should not be used together.

when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:

a) intrauterine device (IUD);

b) surgical sterilization of the partner (vasectomy for 6 months minimum);

c) combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal);

d) progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable);

e) intrauterine hormone releasing system (IUS);

f) bilateral tubal occlusion.

4. Females of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

a) hysteroscopic sterilization;

b) bilateral tubal ligation or bilateral salpingectomy;

c) hysterectomy;

d) bilateral oophorectomy;

**OR** be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status. FSH analysis for postmenopausal women will be done at screening. FSH levels should be in the postmenopausal range as determined by the central laboratory.

5. Non-vasectomized male patient agrees to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study medication and the female partner agrees to comply with inclusion criteria 3 or 4. For a vasectomized male who has had his vasectomy 6 months or more prior to study start, it is required that they use a condom during sexual intercourse. A male who has been vasectomized less than 6 months prior to study start must follow the same restrictions as a non-vasectomized male.
6. If male, patient agrees not to donate sperm from the first dose until 90 days after their last dose.
7. Patients must fall within:
   a) A SARA score of $5 \leq X \leq 33$ points (out of 40)

   **AND**

   b) Either:
      i. Within the 2-7 range (0-8 range) of the Gait subtest of the SARA scale

      **OR**

      ii. Be able to perform the 9-Hole Peg Test with Dominant Hand (9HPT-D) (SCAFI subtest) in $20 \leq X \leq 150$ seconds.
8. Weight ≥15 kg at screening.
9. Patients are willing to disclose their existing medications/therapies for (the symptoms) of NPC, including those on the prohibited medication list. Non-prohibited medications/therapies (e.g. miglustat, concomitant speech therapy, and physiotherapy) are permitted provided:
   a) The Investigator does not believe the medication/therapy will interfere with the study protocol/results
   b) Patients have been on a stable dose/duration and type of therapy for at least 42 days before **Visit 1** (Baseline 1)
   c) Patients are willing to maintain a stable dose/do not change their therapy throughout the duration of the study.
10. An understanding of the implications of study participation, provided in the written patient information and informed consent by patients or their legal representative/parent, and demonstrates a willingness to comply with instructions and attend required study visits (for children this criterion will also be assessed in parents or appointed guardians).

**Exclusion Criteria:**

A patient will not be included in this study if one or more of the following criteria apply:

1. Asymptomatic patients
2. Patient has clinical features of NPC and a positive biomarker screen and/or filipin test, but

a negative result on a previous genetic test for NPC

3. Patients who have any of the following:
    a) Chronic diarrhea;
    b) Unexplained visual loss;
    c) Malignancies;
    d) Insulin-dependent diabetes mellitus.
    e) Known history of hypersensitivity to Acetyl-Leucine (DL-, L-, D-) or derivatives.
    f) History of known hypersensitivity to excipients of Ora-Blend® (namely sucrose, sorbitol, cellulose, carboxymethylcellulose, xanthan gum, carrageenan, dimethiconne, methylparaben, and potassium sorbate).
4. Simultaneous participation in another clinical study or participation in any clinical study involving administration of an investigational medicinal product (IMP; 'study drug') within 42 days prior to **Visit 1**.
5. Patients with a physical or psychiatric condition which, at the investigator's discretion, may put the patient at risk, may confound the study results, or may interfere with the patient's participation in the clinical study.
6. Known clinically-significant (at the discretion of the investigator) laboratories in hematology, coagulation, clinical chemistry, or urinalysis, including, but not limited to:
    a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5x upper limit of normal (ULN);
    b. Total bilirubin >1.5x ULN, unless Gilbert's syndrome is present in which case total bilirubin >2x ULN.
7. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.
8. Current or planned pregnancy or women who are breastfeeding.
9. Patients with severe vision or hearing impairment (that is not corrected by glasses or hearing aids) that, at the investigator's discretion, interferes with their ability to perform study assessments.
10. Patients who have been diagnosed with arthritis or other musculoskeletal disorders affecting joints, muscles, ligaments, and/or nerves that by themselves affects patient's mobility and, at the investigator's discretion, interferes with their ability to perform study assessments.
11. Patients unwilling and/or not able to undergo a 6-week washout period from any of the following prohibited medication prior to **Visit 1** (Baseline 1) and remain without prohibited medication through **Visit 6.**
    a) Aminopyridines (including sustained-release form);
    b) N-Acetyl-DL-Leucine (e.g. Tanganil®);
    c) N-Acetyl-L-Leucine (prohibited if not provided as IMP);
    d) Riluzole;
    e) Gabapentin;
    f) Varenicline;
    g) Chlorzoxazone;

h) Sulfasalazine;

i) Rosuvastatin.

**IMP, Dose and Mode of Administration:**

N-Acetyl-L-Leucine is a powder for oral suspension, being investigated for the treatment of NPC. The study drug contains no excipients.
The study drug is formulated as 1000 mg Powder for suspension in 40 mL Ora-Blend® and oral administration. The suspension vehicle Ora-Blend® contains the following excipients: purified water, sucrose, glycerin, sorbitol, flavoring, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, calcium sulfate, trisodium phosphate, citric acid and sodium phosphate as buffers, dimethicone antifoam emulsion, preserved with methylparaben and potassium sorbate.
The 40 mL of Ora-Blend® will be combined into the powder and must be shaken vigorously for 2 minutes so that it fully mixes before being administered.
During the treatment period of this study, the dosing of the study drug is as follows:

- Adults and children aged ≥13 years in Europe and aged ≥18 years in the United States will take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Children aged 6-12 years weighing 15 to <25 kg will take 2 g per day: 1 g in the morning and 1 g in the evening[35].
- Children aged 6-12 years weighing 25 to <35 kg will take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening[36].
- Children aged 6-12 years weighing ≥35 kg will take 4 per day: 2 g in the morning, 1 g in the afternoon and 1 g in the evening (as per adults)[37].

[redacted]

In the Extension Phase, patients will transition to taking IB1001 formulated as granules for oral suspension in a Sachet.

**Modifications to Scheduled Doses**

On visit days, patients should keep to their usual dosing schedule.

If a patient misses a dose of study drug, the patient should wait and take the next dose according to the treatment schedule.

Compliance will be assessed upon a review of the inventory of IB1001 bottles returned from patients.

The patient's total daily dose may be reduced by up to one-half of their assigned dose at the discretion of the investigator.

In the event a patient turns 13 years old, or a patient aged 6-12 years old changes weight category over the course of the study, their daily dose will not change from the initial dosing regimen prescribed at Visit 2, the start of IMP.

Study drug will be taken during the 42 days (+7 days) treatment period. After the 42 days (+7 days) treatment period, patients will enter a 42-day (+7 days) washout period, which includes efficacy and safety assessments.

[35] European Sites only
[36] European Sites only
[37] European Sites only

**Concomitant Medications and Therapies**

At **Visit 0/Visit 1**, all medication taken in the last 60 days prior to date of informed consent must be recorded. The current amount (in hours per week) of therapy (e.g., physiotherapy, speech therapy) needs to be recorded at the time of informed consent.

**Table 1** lists medications that are prohibited and must not have been used by the patient for at least 42 days before **Visit 1** (for both "naïve" and "non-naïve" patients). Medication not listed in this table will be permitted, at the discretion of the investigator, as long as there is no interference with the study objectives or patient's safety. Doses of medications and therapies used for (the symptoms) NPC should remain as constant as possible (at the investigator's discretion) throughout the trial.

**Table 1: Prohibited Medications**

| Prohibited medication | Washout prior to treatment |
|---|---|
| Aminopyridines (including sustained-release form) | 42 days |
| N-Acetyl-DL-Leucine (e.g. Tanganil®) or N-Acetyl-L-Leucine (if not provided as study drug during the study) | 42 days |
| Riluzole | 42 days |
| Gabapentin | 42 days |
| Varenicline | 42 days |
| Chlorzoxazone | 42 days |
| Sulfasalazine | 42 days |
| Rosuvastatin | 42 days |

**Statistical Methods:**

**Populations for Analysis**

- The Safety Analysis Set (SAF) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine)
- The intention-to-treat analysis set (ITT) will consist of all patients in the Safety Analysis Set with a video recording at either Visit 1 or Visit 2 (or both)
- The modified intention-to-treat analysis set (mITT) will consist of all patients in the SAF with a video recording at either Visit 1 or Visit 2 (or both) and one video recording at either Visit 3 or Visit 4 (or both).
- The Per Protocol Set (PPS) will consist of all patients with video recordings at baseline (Visit 1 or Visit 2), end of treatment (Visit 3 or Visit 4), and end of washout (Visit 5 or Visit 6) and without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variable.

Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

All variables will be summarized using descriptive statistics. The number of patients, mean, standard deviation (SD), minimum, median, and maximum will be calculated for continuous and score variables. Frequency tables will be generated for categorical data.

A one-sided significance level of 5% will be used throughout for all endpoints as a guide for evidence for activity. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance with equal emphasis placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates.

No correction for multiple comparisons will be included.

**Primary Endpoint**

The primary endpoint for the study is based on blinded raters' Clinical Impression of Change in Severity (CI-CS) comparing videos showing the patient's change in performance over 6 weeks on a pre-defined anchor clinical symptom scale: either the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or the 8 Meter Walk Test (8MWT).

The comparison of the Visit 4 video with the Visit 2 video and the comparison of the Visit 6 video with the Visit 4 video will provide the scores that contribute to the primary endpoint. Each of these comparisons will score change on a 7-point Likert scale (+3=significantly improved to -3= significantly worse).

During the pre-treatment period, the treating physician will evaluate each patient's clinical symptoms and select, at **Visit 1,** either the 9HPT-D or 8MWT as the primary anchor around which the CI-CS assessment will be scored. A cognitive assessment should be performed at **Visit 1** according to standard procedures of the clinical site to assist with the selection of the anchoring functional test appropriate for each patient from both a cognitive and a motor perspective.

The primary evaluation of the CI-CS will be performed by two independent raters whose assessments will be based on videos of the anchor test taken at each visit. These raters will be blinded to the treatment periods (baseline, treatment, or washout) to reduce detection and performance bias.

The primary endpoint is defined as the CI-CS comparing end of treatment with N-Acetyl-L-Leucine (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment with N-Acetyl-L-Leucine (Visit 4) based on the primary anchor test.

The CI-CS assessment will instruct the blinded rater to consider: *'compared to the first video, how has the severity of their performance on the 9HPT-D or 8MWT changed (improved or worsened) in 6-weeks as observed in the second video?'*

Each video pairing (CI-CS) will be read by the two independent raters, and the appropriate Likert scale score will be entered onto the eCRF. If there is a difference of one (1) point in the two primary blinded reviewers' CI-CS scores for a specific video pairing, the two scores will be averaged. If there is difference greater than one (1) point between the two primary blinded reviewers' CI-CS scores for a specific video pairing, an adjudication read will be triggered. In such cases, a third blinded reviewer will review the scores given from each of the two primary independent reviewers and determine which score is more accurate, that of reviewer A or reviewer B (adjudication by consensus). The adjudicator's decision will be the final score for that video assessment.

The statistical analysis of this endpoint will utilize a single sample t-test comparing the mean value of the primary endpoint with zero. This endpoint allows the effect N-Acetyl-L-Leucine to be measured both in terms of improvement during treatment followed by any deterioration once treatment is removed.

**Secondary Endpoints**
Supportive secondary endpoints will be evaluated that directly supplement the analysis of the primary endpoint as follows:

- The CI-CS for end of treatment with N-Acetyl-L-Leucine (Visit 4) versus baseline (Visit 2) and end of washout (Visit 6) versus end of treatment with N-Acetyl-L-Leucine (Visit 4) will each be summarized descriptively.
- Improvement in the primary and non-primary anchor test measure will be evaluated based on the change in the blinded raters' Clinical Impression of Severity (CI-S) between baseline (average for Visit 1 and Visit 2) and end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) minus the change in CI-S between end of treatment with N-Acetyl-L-Leucine (average for Visit 3 and Visit 4) and end of washout (average for Visit 5 and Visit 6). The statistical analysis for the primary anchor test CI-S endpoint will be as for the analysis of the primary endpoint. There will be no formal statistical testing of the non-primary anchor test for the CI-S endpoint.
- Sensitivity measurement of change in performance on either the 9HPT-D or the 8MWT on a 3-point scale. Using the CI-CS outcome for the primary anchor test based on the data for **Visits 2** and **Visit 4,** any patient given a score of -1, -2, or -3 on the CI-CS will be classified as worsened (<0). Any patient classified as 0 on the CI-CS will be classified no change (0). Any patient given a score of +1, +2, +3 on the CI-CS will be classified as improved (>0).
- An evaluation of the CI-CS for the test (9HPT-D or 8MWT) that was not selected as the primary anchor test will also be undertaken. This will enable the separate analysis of CI-CS for both the 9HPT-D and the 8MWT.

Each individual video (CI-S) will also be read by the two independent raters. For the CI-S, if there is one (1) point or more in the two blinded reviewers scores, the two scores will still be averaged.

Additional secondary endpoints will investigate other measures of symptoms and quality of life. Descriptive statistics will be provided for these measures at each visit and also changes from baseline (**Visit 2**) to the end of treatment with N-Acetyl-L-Leucine (**Visit 4**), as well as end of treatment with N-Acetyl-L-Leucine (Visit 4) to the end of post-treatment washout (**Visit 6**) for the following measures:

- Spinocerebellar Ataxia Functional Index (SCAFI)[38]
- Scale for Assessment and Rating of Ataxia (SARA) score

[38]The 9-hole Peg Test of the Dominant Hand (9HPT-D) and the 8-meter Walk Test (8MWT), will be videoed for every patient at every visit, except Visit 0.

- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[39] for children aged <18 years (visual analogue scale; descriptive system)
- Modified Disability Rating Scale (mDRS)
- Treating Physician Clinical Global Impression of Severity (CGI-S) at every visit
- Treating Physician Clinical Global Impression of Change (CGI-C) comparing end of treatment (**Visit 4**) to baseline (**Visit 2**), and end of washout (**Visit 6**) to end of treatment (**Visit 4**)
- Caregiver Clinical Global Impression of Severity (CGI-S) at every visit
- Caregiver Clinical Global Impression of Change (CGI-C) comparing end of treatment (**Visit 4**) to baseline (**Visit 2**), and end of washout (**Visit 6**) to end of treatment (**Visit 4**)
- Patient Clinical Global Impression Scales Impression of Severity (CGI-S) at every visit *if they are able*
- Patient Clinical Global Impression of Change (CGI-C) comparing end of treatment (**Visit 4**) to baseline (**Visit 2**), and end of washout (**Visit 6**) to end of treatment (**Visit 4**) *if they are able*

The SARA total score, the SCAFI total score, the individual SCAFI subtests: 9 Hole Peg Test with the Dominant Hand (9HPT-D), 8 Meter Walk Test (8MWT), and PATA test, will be evaluated statistically based on a single sample t-test or a single sample Wilcoxon Signed Rank test.

The individual SCAFI subtest: 9 Hole Peg Test with Nondominant hand (9HPT-ND), and the mDRS will be evaluated descriptively.

All CGI-S measures, and caregiver and patient CGI-C measures will be summarised descriptively. The physician's CGI-C measures will be analysed as for the CI-CS primary endpoint.

The measures of the two indices (-5L and -Y) of the EQ-5D descriptive system and measures of the two indices (-5L and -Y) of the EQ-5D visual analogue scale (VAS) will be evaluated descriptively.

**Exploratory Endpoints**

Sparse PK sampling will be collected to characterize the pharmacokinetics of N-Acetyl-L-Leucine in patients with NPC.

**Determination of Sample Size**

It is postulated that N-Acetyl-L-Leucine will show effectiveness in 30% of patients and this success rate is viewed as being clinically important. Assuming that this group of patients will have scores that are evenly distributed across the values 1 and 2 for the primary endpoint and further that the remaining 70% of patients will have scores that are evenly distributed between the values -1, 0, and 1. The resulting mean score is 0.45 and the standard deviation (SD) for the primary endpoint under these assumptions is then 1.02. With 30 patients reporting on the primary endpoint, the study will have 76% power to detect a treatment benefit in a 5% one- sided one-sample t-test.

**Significance Level and Multiplicity**

A one-sided significance level of 5% will be used throughout for all endpoints as a guide for evidence for activity. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance with equal emphasis placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates.
No correction for multiple comparisons will be included.

[39] European sites only

**Missing Data**

The primary endpoint will utilise assessments based on single video recordings at the end baseline period (**Visit 2**), end of the treatment period (**Visit 4**), and end of the washout period (**Visit 6**). If the **Visit 2** video is missing, the **Visit 1** video will be used in its place. Similarly, if the **Visit 4** and **Visit 6** videos are missing, **Visit 3** and **Visit 5** videos will respectively be used in their place.

Analyses based on the mITT analysis set will utilise a last observation carried forward (LOCF) approach for missing at Visit 5 and Visit 6. For the primary endpoint CI-CS this implies that the CI-CS value for **Visit 4** to **Visit 6** will be assigned the value 0 (stable) if both videos at Visit 5 and Visit 6 are unavailable.

Additional methods to deal with missing data will be detailed in the Statistical Analysis Plan (SAP). Any changes from the SAP will be described and justified in the Clinical Study Report.

**Subgroup Evaluation**

For each of the primary and additional secondary endpoints there will be separate analyses within key subgroups. These subgroups will be detailed in the SAP.

**Meta-analysis**

Separate trials will be conducted for NPC, *GM2-gangliosidosis* (Tay-Sachs and Sandhoff disease), and ataxia-telangiectasia. There will however be a series of meta-analyses that will bring together the data from the studies for the primary and secondary endpoints. Further details will be provided in a Meta-Analysis Statistical Analysis Plan (MASAP).

Sparse PK sampling is exploratory/descriptive.

**COVID-19**

This study is conducted during the COVID-19 outbreak. Data capture decisions have been taken due to national, local, or site-specific restrictions imposed due to COVID-19, with the primary need to prioritize the safety of clinical study teams and patients, and to maintain the integrity of the study/data collection.

The complete impact of COVID-19 on the proposed statistical analyses is unknown. The statistical analysis plan already contains policies for handling missing data, however. Specific items/changes related to COVID-19 are being detailed in a separate document to the SAP (for the Parent Study, Addendum 1), which will be maintained throughout the study continuation and adjusted as needed based on the duration and extent of the impact of the COVID-19 situation.

**Relevant safety related alerts/Withdrawal Criteria:**

The Data Safety Monitoring Board (DSMB), in conjunction with the study Medical Monitor and/or Sponsor, is responsible for the oversight of safety. For this purpose, the DSMB will receive regular updates of safety.

The DSMB will review all safety data on a regular basis. The exact content of review material and the frequency of review will be detailed in the DSMB charter.

The DSMB will also be involved in risk-assessments of the impact of COVID-19, and reviewing any guidance issued by the Sponsor in regard to the global pandemic. The DSMB may be asked to give recommendations on the conduct of trial operations and protocol adjustments which may be required in light of COVID-19.

**Patient Withdrawal**

Patients may withdraw from the study at any time at their own request without stating the reason(s) for withdrawal. If a patient withdraws early from the study after start of treatment an early termination (ET) visit should be arranged, preferably 7-14 days after the last dose of study drug.

"Non-naïve" patients (including "naïve" patients reclassified as "non-naïve") will be withdrawn from the study if their urine sample from **Visit 1** (Baseline 1) detects levels of N-Acetyl-D-Leucine above the permitted threshold.

The treating physician may decide that a patient should be withdrawn from the study or from the study drug. Reasons for withdrawal from the study or the study drug may include, but are not limited to, the following:

- Development of any adverse event (AE), serious AE (SAE), laboratory abnormality, condition, intercurrent illness, injury, medical condition, or use of a medication that is likely to interfere with patient safety, the overall assessment, or the study procedures, such that continued participation in the study would not be in the best interest of the patient.
- Consent withdrawal.
- The patient becomes pregnant or plans to become pregnant.
- Significant patient noncompliance, defined as an unwillingness to complete the procedures defined in the Schedule of Assessments.
- Patient lost to follow-up (i.e., staff unable to contact patient after several attempts).
- Investigator, Medical Monitor, and/or Sponsor decision for any other reason not listed above that may invalidate the results of the study or jeopardizes the health and/or safety of a patient.
- Complications related to pandemics such as COVID-19.

Patients who discontinue study drug prior to completing the full treatment period, should be asked to complete the remaining study visits as far as possible and complete safety assessments at a minimum. If unwilling to complete the remaining study visits, regardless of the reason for withdrawal, best efforts should be made to have the patient take part in early termination (ET) procedures, preferably 7-14 days following the last dose of the study drug, unless the patient is lost to follow-up or has withdrawn his/her consent to further study participation.

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[redacted]

## 13.2 Appendix 2: List of Institutions Involved in the Study

| | |
|---|---|
| **Sponsor** | IntraBio Ltd. [redacted] |
| **Sponsor's Medical Expert** | [redacted] |
| **Data Management** | [redacted] |
| Electronic Case Report Form (eCRF) | [redacted] |
| **Medical Monitor** | [redacted] |

**Biostatistician**

[redacted]

**Adverse Event Reporting**

[redacted]

**Central Laboratory**

[redacted]

**PK laboratory**

[redacted]

**PK Modeling**

[redacted]

**IMP Manufacturing**

[redacted]

[redacted]

**IMP Packaging, Labeling, Distribution**

[redacted]

[redacted]

**Videotaping**

[redacted]

## 13.3 Appendix 3: Schedule of Events

| Period | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **2 Weeks** | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening/Bsl 1** | **Baseline 2** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -14* | *Day 1, Start IMP* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *XX* |
| **Visit Window allowed** | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+ 7days* | *na* |

## Appendix 3A – Schedule of Events for "Naïve" Patients

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patient information and informed consent process | X | | | | | X[19] | |
| Inclusion / exclusion criteria | X | X | | | | X[19] | |
| Patient weight and height measurements | X | | | | | | |
| Confirmation prohibited medications have not been used in the past 42 days | X | X[3,4] | | | | | |
| Classify patient as "Naïve" or "Non-naïve" | X | | | | | | |
| Patient demographics (in accordance with local regulations) | X | | | | | | |
| Relevant medical history | X | | | | | | |
| 60-Day drug history | X | | | | | | |
| Documentation of therapy | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X |
| 12-lead electrocardiogram (ECG)[5] | X | | X | | X | | X |
| Urine test for N-Acetyl-D-Leucine[6] | X[7] | X | | | X | X | X |
| Blood safety laboratory tests[8] | X | X | X | X | X | X | X |
| Follicle stimulating hormone serum [8, 9] | X | | | | | | |
| Urinalysis [8] | X | X | X | X | X | X | X |
| Urine by dipstick for pregnancy test[10] | | X | | X | | X | X |

| Period | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **2 Weeks** | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening/Bsl 1** | **Baseline 2** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -14* | *Day 1, Start IMP* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *XX* |
| **Visit Window allowed** | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+ 7days* | *na* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Blood sample for sparse PK [6] | X | X | X | X | X | X | X |
| Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[11] for children aged <18 years | X | X | X | X | X | X | X |
| Scale for Ataxia Rating (SARA) | X | X | X | X | X | X | X |
| Modified Disabling Rating Score (mDRS) | X | X | X | X | X | X | X |
| Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS) | X | | | | | | |
| Scale for Spinocerebellar Ataxia Functional Index (SCAFI)[12] | X | X | X | X | X | X | X |
| Cognitive assessment according to standard procedures of the clinical site | X | | | | | | |
| Determination of CI-CS Primary Anchor Test (9HPT-D or 8MWT) | X | | | | | | |
| Clinical Global Impression of Severity (CGI-S) by Physician | X | X | X | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Caregiver | X | X | X | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Patient[13] | X | X | X | X | X | X | X |
| Clinical Global Impression of Change (CGI-C) by Physician | | | | X | | X | X |
| Clinical Global Impression of Change (CGI-C) by Caregiver | | | | X | | X | X |
| Clinical Global Impression of Change (CGI-C) by Patient[13] | | | | X | | X | X |

| Period | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **2 Weeks** | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening/Bsl 1** | **Baseline 2** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -14* | *Day 1, Start IMP* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *XX* |
| **Visit Window allowed** | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+ 7days* | *na* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Medication History: Confirm if N-Acetyl-Leucine ever used for "naïve" patients | | | | | | X | X |
| Documentation of concomitant medication[14] | X | X | X | X | X | X | X |
| Documentation of AEs | X | X | X | X | X | X | X |
| Dispensing of study drug | | X | X[15] | | | | |
| Intake of study drug at site | | X[16] | | | | | |
| Return of study drug | | | X | X | | | X |
| Study drug compliance check | | | X[17] | X[18] | | | X[18] |

[1] If the patient's eligibility is confirmed and their urine screen for N-Acetyl-D-Leucine is below the permitted threshold. The next visit, **Visit 2,** should be planned 14 days (+7 days) from **Visit 1.**

[2] All assessments must be done pre-dose

[3] At **Visit 2,** confirm no prohibited medications since **Visit 1**

[4] If the patient (or caregiver) states the patient has been using prohibited medication at **Visit 2,** they will be classified as non-compliant and withdrawn from the study

[5] If feasible, repeat assessments performed at treating physician's discretion if clinically significant results at **Visit 3**

[6] To be analyzed at PK lab

[7] If the patient's urine sample unexpectedly detects levels of N-Acetyl-D-Leucine above the permitted threshold, they will (provided eligible) switch to "non-naïve"

[8] To be analyzed at the central lab

[9] Only for post-menopausal women of non-child bearing potential with amenorrhea for at least 1 year prior to the first dose (and have not undergone sterilization procedures at least 6 months prior to the first dose)

[10] Only for women of childbearing potential; done at site

[11] In Europe only

[12] Two subtests, the 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videoed in a standardized format at every visit (except Visits 0).

[13] If the patient is able to provide the CGI-S/C

[14] Any concomitant medication needs to be recorded, used or not used for (symptoms of) NPC since the last 60 days prior to date of informed consent, up to End of Study / ET

[15] If needed

[16] Patient should not have used any of the prohibited concomitant medication 42 days prior to first dose of study drug, and have had a urine screen for N-Acetyl-D-Leucine below the permitted threshold prior to first dose of study drug.

[17] If feasible

[18] Or after the Visit if IMP is returned via courier

[19] If Investigator determines continued treatment with IB1001 in patient's best interest, and patient would like to participate in the optional Extension Phase, task performed for continuation into the Extension Phase

*General note: due to COVID-19, deviations from the schedule of visits and assessments may be necessary, i.e. visits may be skipped, postponed, or performed remotely. See Section 3.1.2 for details*

| | Study Run-In | | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| | Screening visit | Pre-treatment Washout | | | | | | | |
| **Duration of the whole period** | **1 Day** | **6 Weeks** | **2 Weeks** | | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 0** | | **Visit 1[1]** | **Visit 2[2]** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening** | | **Baseline 1** | **Baseline 2/ Start IMP** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -56* | | *Day -14* | *Day 1* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *na* |
| **Visit Window allowed** | *na* | | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *na* |

## Appendix 3B: Schedule of Events for "Non-naïve" Patients

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient information and informed consent process | X | | | | | | | | |
| Inclusion / exclusion criteria | X | | X | X | | | | X[19] | |
| Patient weight and height measurements | X | | | | | | | X[19] | |
| Confirmation prohibited medications have not been used in the past 42 days at Visit 1/since Visit 1 for Visit 2 | | | X | X[3] | | | | | |
| Confirmation prohibited medications have been used within past 42 days[4] | X | | | | | | | | |
| Classify patient as "Naïve" or "Non-naïve" | X | | | | | | | | |
| Patient demographics (in accordance with local regulations) | X | | | | | | | | |
| Relevant medical history | X | | | | | | | | |
| 60-Day drug history | X | | | | | | | | |
| Documentation of therapy | X | | X | X | X | X | X | X | X |
| Vital signs | X | | X | X | X | X | X | X | X |
| 12-lead electrocardiogram (ECG)[5] | | | X | | X | | X | | X |

| | Study Run-In | | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| | Screening visit | Pre-treatment Washout | | | | | | | |
| **Duration of the whole period** | **1 Day** | **6 Weeks** | **2 Weeks** | | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 0** | | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening** | | **Baseline 1** | **Baseline 2/ Start IMP** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -56* | | *Day -14* | *Day 1* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *na* |
| **Visit Window allowed** | *na* | | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *na* |
| Urine Test for N-Acetyl-D-Leucine[6] | | | X[7] | X | | | X | X | X |
| Blood safety laboratory tests[8] | | | X | X | X | X | X | X | X |
| Follicle stimulating hormone serum[9] | | | X | | | | | | |
| Urinalysis[8] | | | X | X | X | X | X | X | X |
| Urine by dipstick for pregnancy test[10] | | | | X | | X | | X | X |
| Blood sample for sparse PK[6] | | | X | X | X | X | X | X | X |
| Quality of Life EQ-5D-5L for patients aged ≥18 years; EQ-5D-Y[11] for children aged <18 years | | | X | X | X | X | X | X | X |
| Scale for Ataxia Rating (SARA) | X | | X | X | X | X | X | X | X |
| Modified Disabling Rating Score (mDRS) | | | X | X | X | X | X | X | X |
| Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS) | | | X | | | | | | |
| Scale for Spinocerebellar Ataxia Functional Index (SCAFI)[12] | X | | X | X | X | X | X | X | X |
| Cognitive assessment according to standard procedures of the clinical site | | | X | | | | | | |

| | Study Run-In | | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| | Screening visit | Pre-treatment Washout | | | | | | | |
| **Duration of the whole period** | **1 Day** | **6 Weeks** | **2 Weeks** | | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 0** | | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening** | | **Baseline 1** | **Baseline 2/ Start IMP** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -56* | | *Day -14* | *Day 1* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *na* |
| **Visit Window allowed** | *na* | | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *na* |
| Determination of CI-CS Primary Anchor Test (9HPT-D or 8MWT) | | | X | | | | | | |
| Clinical Global Impression of Severity (CGI-S) by Physician | | | X | X | X | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Caregiver | | | X | X | X | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Patient[13] | | | X | X | X | X | X | X | X |
| Clinical Global Impression of Change (CGI-C) by Physician | | | | | | X | | X | X |
| Clinical Global Impression of Change (CGI-C) by Caregiver | | | | | | X | | X | X |
| Clinical Global Impression of Change (CGI-C) by Patient[13] | | | | | | X | | X | X |
| Documentation of concomitant medication[14] | X | | X | X | X | X | X | X | X |
| Documentation of AEs | X | | X | X | X | X | X | X | X |
| Dispensing of study drug | | | | X | X[15] | | | | |
| Intake of study drug at site | | | | X[16] | | | | | |
| Return of study drug | | | | | X | X | | | X |
| Study drug compliance check | | | | | X[17] | X[18] | | | X[18] |

| | Study Run-In | | Baseline Period | | Treatment Period | | Wash-Out Period | | Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| | Screening visit | Pre-treatment Washout | | | | | | | |
| **Duration of the whole period** | **1 Day** | **6 Weeks** | **2 Weeks** | | **6 Weeks** | | **6 Weeks** | | **1 Day** |
| **Visit number** | **Visit 0** | | **Visit 1**[1] | **Visit 2**[2] | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / EOS** | **ET** |
| **Name of the Visit** | **Screening** | | **Baseline 1** | **Baseline 2/ Start IMP** | **Treatment 1** | **Treatment 2** | **Washout 1** | **Washout 2** | **ET** |
| **Timeline (Days)** | *Day -56* | | *Day -14* | *Day 1* | *Day 28* | *Day 42* | *Day 70* | *Day 84* | *na* |
| **Visit Window allowed** | *na* | | *na* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *+7 days* | *na* |

[1] If the patient's eligibility is confirmed and their urine screen for N-Acetyl-D-Leucine is below the permitted threshold. The next visit, **Visit 2,** should be planned 14 days (+7) days from Visit 1.

[2] All assessments must be done pre-dose

[3] At **Visit 2,** confirm no prohibited medications since **Visit 1**

[4] If the patient (or caregiver) states the patient has been using prohibited medication at **Visit 1** or **Visit 2,** they will be classified as non-compliant and withdrawn from the study

[5] If feasible, repeat assessments performed at treating physician's discretion if clinically significant results at **Visit 3**

[6] Analyzed at PK lab

[7] Patients whose Visit 1 urine sample detects limits of N-Acetyl-D-Leucine above the permitted threshold are classified as non-compliant and withdrawn from the study

[8] Analyzed at central lab

[9] Only for post-menopausal women of non-child bearing potential with amenorrhea for at least 1 year prior to the first dose (and have not undergone sterilization procedures at least 6 months prior to the first dose)

[10] Only for women of childbearing potential; done at site

[11] In Europe only

[12] At Visit 1 through Visit 6 (*not* Visit 0), two subtests, the 9-hole Peg Test of the Dominant Hand (9HPT-D) and 8-meter Walk Test (8MWT) will be videoed in a standardized format at every visit. From **Visit 2**, the selected anchor test (9HPT-D or 8MWT) is to be performed first, before the remaining SCAFI subsets.

[13] If the patient is able to provide the CGI-S/C

[14] Any concomitant medication needs to be recorded, used or not used for (symptoms of) NPC since the last 60 days prior screening, up to End of Study / ET

[15] If needed

[16] Patient should not have used any of the prohibited concomitant medication 42 days prior to first dose of study drug, and have had a urine screen for N-Acetyl-D-Leucine below the permitted threshold prior to first dose of study drug.

[17] If feasible

[18] Or after the Visit if IMP is returned via courier

[19] If Investigator determines continued treatment with IB1001 in patient's best interest, and patient would like to participate in the optional Extension Phase, task performed for continuation into the Extension Phase

*General note: due to COVID-19, deviations from the schedule of visits and assessments may be necessary, i.e. visits may be skipped, postponed, or performed remotely. See Section 3.1.2 for details*

### 13.4 Appendix 4: Rationale for the Clinical Impression of Change in Severity (CI-CS)

Detailed rational for the development, administration, and scoring of the primary Clinical Impression of Change in Severity (CI-CS) endpoint is located in the supplementary document "Clinical Impression of Change in Severity. Administration and Scoring Manual" [Fields, 2020].

### 13.5 Appendix 5: Protocol Amendment History

The Protocol Amendment Summary of Changes is located in the supplementary document, “IB1001-201 Protocol Summary of Changes Version 2.0, 10-OCT-2022”. An overview of the Protocol Version history is located directly before the Table of Contents (TOC).

### 13.6 Appendix 6: Extension Phase

# 1 Introduction – Extension Phase

This Extension Phase allows patients who have completed Visit 6 of the Parent Study of IB1001-201 to, at the discretion of the Principal Investigator (PI), continue treatment with N-Acetyl-L-Leucine (IB1001) if the PI determines it is in their best interest. The overall design is presented in Section 3.1.2[40].

The Extension Phase will be conducted at clinical sites that participated in the Parent Study, and in countries that have regulatory and ethics/institutional review board approval for the Extension Phase. The primary eligibility criteria for a patient to enter the Extension Phase is the participation and completion of the IB1001-201 study with IB1001.

The Extension Phase will assess patients after one-year of treatment with IB1001, followed by a 42-day (+14 day) washout. After the 42-day Extension Phase washout (Visit 10), at the discretion of the Principal Investigator (PI), patients will be able to continue treatment with N-Acetyl-L-Leucine (IB1001) for an additional 1-year if the PI determines it is in their best interest.

The Extension Phase will collect information on the long-term safety, tolerability, pharmacokinetics (PK), and efficacy of IB1001 as a treatment for NPC for the purpose of further assessing the risk/ benefit balance of the investigational medicinal product in the proposed clinical setting.

## 1.1 Risk/Benefit Considerations

NPC is a rare, serious, and life-threatening indication that predominantly affects the pediatric population. Treatment of NPC is so-far limited to symptomatic management and miglustat (Zavesca™) (which is not approved in the US). Therefore, there is a strong need for the development of novel and more effective therapies to treat this disease.

The active ingredient in IB1001 is N-Acetyl-L-Leucine, an acetylated derivate of a ubiquitously present amino acid occurring in human food. N-Acetyl-L-Leucine is also an endogenously generated metabolite of L-Leucine.

Appropriate patient selection is one factor in considering the balance of risks of adverse events (AEs) against potential clinical benefit. Patients will only be considered for the Extension Phase, if they have completed the Parent Study and the PI determined continued treatment with N-Acetyl-L-Leucine to be in the patient's best interest.

Based upon the very good safety profile of N-Acetyl-L-Leucine (and N-Acetyl-DL-Leucine) observed in animals at dose levels up to the limit dose ([redacted]) as well as knowledge of safe use of N-Acetyl-DL-Leucine in children as young as 9 months of age [Picone, 2018], inclusion of children aged 6 years and over who took part in the Parent Study is judged to be safe. Women of childbearing potential and partners of women of childbearing potential will continue to be required to adhere to

[40] Sections referenced in Appendix 6 refer to the Appendix 6 Sections, unless otherwise indicated by "..of the Parent Study"

strict precautions to prevent pregnancy. Women who are pregnant, breast-feeding, or planning to become pregnant will be excluded from the study. In addition, a negative pregnancy test will be a prerequisite for the inclusion of women of child bearing potential and urine pregnancy tests will be carried out at each visit of the Extension Phase.

*Levels of risk and burden on participants*

N-Acetyl-L-Leucine is being developed for the treatment of adults and children with NPC, a rare and ultimately fatal disorder that predominantly affects pediatric patients [Vanier, 2010; Utz et al, 2017]. As described in Section 1.1 of the Parent Study, published case series and long-term use of N-Acetyl-DL-Leucine in patients with NPC suggest the prospect of a direct benefit to the participating patients over standard of care.

To ensure the feasibility of this trial, NPC clinical experts [ ] and the heads of multinational NPC patient organizations [ .] were consulted and involved in its design.

The degree of burden to participants in the Extension Phase is defined by the description of assessments in Section 7.

The behavioral tests for evidence of efficacy are routinely used in the evaluation of NPC and are relatively fast to perform, with the individual subtests of the SCAFI rarely taking more than 2 minutes for patients with NPC to complete [Bremova et al, 2015]. The Scale for Assessment and Rating of Ataxia (SARA) takes about 15 minutes and the Niemann-Pick type C Clinical Severity Scale (NPC-CSS) takes about 45 minutes to complete [ ]. The use of these tests was determined together with representatives of the patient community and parents of patients with NPC and Tay-Sachs disease, as being clinically meaningful for the patients and families and reflective of the ability to perform acts of everyday life safety and securely, while at the same time not being exhausting [ ].

To minimize patient fatigue, visits with PK sampling may be conducted over two days, with the blood draws for PK taken on the day after the behavioral tests. Topical anesthesia may be applied before blood sampling. The total amount of blood taken per subject during the Extension Phase is provided in Section 6.5.5. Patients will be ≥15 kg and the total blood volume taken in accordance with the maximum allowable research-related blood sample volumes provided in the incoming EU ethical considerations for clinical trials on medicinal products conducted with minors [EudraLex Volume 10, 2017].

The impact of the interventions will be assessed by patient-reported outcomes (measurement of global impression, see Section 6.1.5 of the Parent Study), where feasible, and quality of life assessments (EQ-5D-5L and EQ-5D-Y, see Section 6.1.3 of the Parent Study).

The investigator will monitor the degree of stress to patients and the risk threshold throughout the trial. Patients will be instructed to report any AEs that they experience to the Investigator and the Investigator will ask about the occurrence of AEs at each visit. As described in Section 11.6 of the Parent Study, if the Investigator (or the Sponsor or Medical Monitor) becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the clinical study may be terminated after appropriate consultation between the involved parties.

In addition, as described in Section 11.5 of the Parent Study, the Data Safety Monitoring Board (DSMB), in conjunction with the study Medical Monitor and/or Sponsor, will monitor the level of risk on a regular basis throughout the study. The DSMB is a multidisciplinary group consisting of clinicians with pediatric experience and a biostatistician. The DSMB has been set up to safeguard the interests of study participants by providing an independent review of patient safety data to monitor that no undue harm is occurring to patients due to their participation. The DSMB may recommend changes in the conduct of the studies to IntraBio, if needed, to ensure the safety of patients in the study and the proper conduct of the studies. The DSMB may also recommend suspending recruitment or terminate the study early because of undue safety risks to patients or any issues concerning the rights of patients. For this purpose, the DSMB will receive regular updates of safety and review all safety data on a regular basis.

Based upon the nature of the drug, the available non-clinical and clinical data for N-Acetyl-L-Leucine and N-Acetyl-DL-Leucine, the current lack of effective treatments for NPC, and in the context of a marketed racemate, this clinical trial is concluded to pose acceptable levels of risk and burden on participants.

*Extension Phase Treatment Period II*
Protocol Amendment 6.0 introduced an additional year of dosing upon completion of the extension-phase washout Visit 10. Extension Phase Treatment Period II will provide additional information on long-term safety and tolerability of IB1001 while allowing patients to have further access to IB1001 for an additional one-year period. Based on the nature of the drug and previous non-clinical and clinical findings (as detailed in Section 1 of the Parent Study) and the safety profile observed in this ongoing study (and in other ongoing IB1001 clinical trials) to date, the risk of allowing patients who have completed the first year of extension-phase dosing, and who agree to continue in the study, is considered acceptable.

## 2 STUDY OBJECTIVES – EXTENSION PHASE

All endpoints in the extension phase are considered secondary to those in the Parent Study.

### 2.1 Primary Objective

The primary objective in the Extension Phase is to evaluate the efficacy of N-Acetyl-L-Leucine based on the 5-Domain Niemann-Pick type C Clinical Severity Scale (NPC-CSS).

### 2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the long-term safety and tolerability of N-Acetyl-L-Leucine at 4 g/day in patients aged ≥13 years, and weight-tiered doses in patients 6 to 12 years of age, with NPC
- To characterize the pharmacokinetics (PK) of N-Acetyl-L-Leucine in patients with NPC

### 2.3 Exploratory Objectives

The exploratory objectives are:

- To assess the clinical efficacy of long-term treatment with N-Acetyl-L-Leucine on symptoms, functioning, and quality of life for patients with NPC
- To assess the effects of a 42-day (+14 days) washout from N-Acetyl-L-Leucine after one-year treatment on symptoms, functioning, and quality of life for patients with NPC

# 3 OVERALL DESIGN AND PLAN OF THE EXTENSION PHASE

## 3.1 Overview

### *3.1.1 Trial Design/Patient Population*

This Extension Phase will enroll patients who have completed Visit 6 of the parent study phase of IB1001-201. Patients will be offered the opportunity to participate in this Extension Phase if the safety and tolerability during the 42-day (+7 days) treatment period of the parent study are considered to be acceptable by their Principal Investigator (PI) and the PI determines further treatment with IB1001 to be in the patient's best interest.

Recruitment into the Extension Phase will continue until all patients who participated in the parent study, and who are willing and eligible to participate in the Extension Phase, are enrolled.

Section 4 contains more detailed information on the eligibility criteria for the Extension Phase.

### *3.1.2 Study Design*

Patients will be assessed approximately 6 times over a 116-week period: at the start of the Extension Phase, after 6 months of treatment, 1 year of treatment, after a 42-day (+14 day) post-extension-phase treatment washout, after 6 months of resuming treatment, and after 1 year of resuming treatment.

Section 7 contains detailed information on the study assessments and procedures that will be conducted at each study phase and visit.

#### *3.1.2.1 Baseline Visit of the Extension Phase*

Preferably, the first visit of the Extension Phase (Visit 7 Part A and Part B; Baseline Visit) should be conducted 1 day (+6 days) after Visit 6, the end of the parent study.

The assessments comprising Visit 7 may be conducted over a two-day period ("Part A" and "Part B")[41]. If Visit 7, Part B is scheduled 1 day (+6 days) after Visit 6 (Washout 2 of the parent study), the assessments conducted at Visit 6 should count as Visit 7, Part A (i.e. the assessments do not need to be repeated).

If **Visit 7B** cannot be scheduled 1 day (+6 days) after Visit 6, the assessments included in Visit 7, Part A and Visit 7, Part B may be performed over two consecutive days, i.e. Visit 7B occurs +1 day after Visit 7A.

During **Visit 7, Part B**, after all efficacy assessments have been performed, the patient will take the first Extension-Phase dose of N-Acetyl-L-Leucine on site.

#### *3.1.2.2 Extension Phase Treatment Period I*

From **Visit 7B** onward**,** all patients will receive treatment with N-Acetyl-L-Leucine for 365 days (+/-14 days).

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[41] If Visit 7 is conducted within +7 days of Visit 6, the assessments performed at "Part A" do not need to be duplicated and Visit 7 will be conducted over one day only.

**Visit 8** will occur at Day 180 (+/-14 days).

**Visit 9, Part A** will occur at Day 365 (+/-14 days).

**Visit 9, Part B** should occur on the day after **Visit 9, Part A**

#### 3.1.2.3 Extension Phase Washout Period

After **Visit 9**, all patients will enter a 42-day (+14 days) washout phase.

**Visit 10** will occur at Day 407 (+ 14 days)

*3.1.2.4 Extension Phase Treatment Period II*

From **Visit 10** onward, all patients will receive treatment with N-Acetyl-L-Leucine for 365 days (+/-14 days).

**Visit 11** will occur at Day 587 (+/-14 days).

**Visit 12** will occur at Day 767 (+/-14 days).

### *3.1.3 Centers*

The trial will be conducted in clinical trial centers that participated in parent study and continue to meet the requirements for performing the planned trial-related investigations. The Extension Phase will only be conducted in countries/study centers where regulatory and Independent Ethics Committee/Institutional Review Board approval has been granted for the Extension Phase.

### *3.1.4 Study Duration*

The treatment and washout duration for all patients, from the first day of dosing with the study drug during the Extension Phase **(Visit 7)** to the final follow-up visit (**Visit 12),** is expected to be approximately 767 days.

## 3.2 Discussion of Study Design

### *3.2.1 Choice of the Primary Endpoint*

The primary endpoint in this Extension Phase is success measured on the 5-domain Niemann-Pick disease type C Clinical Severity Scale (NPC-CSS) from the Extension Phase baseline (Visit 7) to the end of treatment in the Extension Phase (Visit 9).

### *3.2.2 Choice of the Secondary Endpoints*

Full PK sampling will be conducted during the Extension Phase.

### *3.2.3 Choice of the Exploratory Endpoints*

All endpoints in the Extension Phase are considered secondary to those in the Parent Study.

In the parent study, the Niemann-Pick type C Clinical Severity Scale (NPC-CSS) was not included as an endpoint, as this measure was considered not sensitive enough to detect changes after 6 weeks of treatment (see Section 3.2.3 of the Parent Study).

Given the extended duration of treatment in the Extension Phase, the NPC-CSS will be introduced as an endpoint, where the graduation of changes is expected to detect clinically relevant changes in functioning / benefit after one year of treatment.

The NPC-CSS was designed to be a measure to characterize and quantify disease progression and is applicable to assess the long-term treatment effects of an interventional therapy [Yanjanin et al, 2010].

Exploratory endpoints in this Extension Phase may also be based on the following timepoints:

- The beginning of the Extension Phase (Visit 7) to the end of the Extension Phase washout period (Visit 10)
- The end of the Extension Phase treatment period I (Visit 9) to the end of the Extension Phase washout period (Visit 10).
- The end of the Extension Phase washout (Visit 10) to the end of the Extension Phase treatment period II (Visit 12)
- The beginning of the Parent study (Visit 1) to the end of the Extension Phase treatment period II (Visit 12)[42]

The exploratory endpoints are defined in Section 8.5.2.

#### *3.2.4 Dose/ Duration of Treatment*

The purpose of the Extension Phase is to give patients who participated in the Parent Study, and whose investigators believe may benefit from continued treatment with IB1001, the opportunity to further access N-Acetyl-L-Leucine once the parent study has been completed. During the Extension Phase, long-term safety and efficacy data will be recorded. In order to be eligible for the Extension Phase, the investigator must also be of the opinion that this is in the patient's best interest.

As discussed in Section 1.1, on the basis of the chemical nature of N-Acetyl-L-Leucine, available non-clinical and clinical evidence, and post marketing experience with the racemate (including compassionate use in NPC), it is considered justifiable from a safety point-of-view to dose for an additional year. This will provide patients continued access to drug while other patients complete the Parent Study and the results from the symptomatic study with a 6-week treatment period are generated (including the blinded rater review) and analyzed.

### 3.3 End of Study Definition

A patient is considered to have completed the Extension Phase if he/she has completed all routine visits of the Extension Phase including the last visit (**Visit 12**).

The end of the study (Parent Study + Extension Phase) is defined as the date of the last visit of the last patient in Study IB1001-201 globally.

[42] Additional exploratory analysis may be conducted to analyze change in outcome assessments over the patients' entire duration of participation in the IB1001-201 clinical trial. Procedures will be defined in the statistical analysis plan (SAP).

# 4 STUDY POPULATION – EXTENSION PHASE

The study population comprises patients with NPC who have completed **Visit 6** of the parent study of IB1001-201. To be eligible, patients must satisfy the following entry criteria:

## 4.1 Inclusion Criteria

1. Completed Visit 6 of the IB1001-201 Parent Study
2. The Principal Investigator determines further treatment with IB1001 to be in patient's best interest
3. Written informed consent signed by the patient and/or their legal representative/parent/ impartial witness for participation in the Extension Phase
4. Patients are willing to continue to remain without the following prohibited medication from **Visit 6** throughout the duration the Extension Phase**:**
    a) Aminopyridines (including sustained-release form);
    b) N-Acetyl-DL-Leucine (e.g. Tanganil®);
    c) N-Acetyl-L-Leucine (prohibited if not provided as investigational medicinal product [IMP]);
    d) Riluzole;
    e) Gabapentin;
    f) Varenicline;
    g) Chlorzoxazone;
    h) Sulfasalazine;
    i) Rosuvastatin.

## 4.2 Patient Withdrawal

Patients may withdraw from the study at any time at their own request, without stating the reason(s) for withdrawal. The policies/procedures for patient withdrawal are defined in Parent Study in Section 4.3.

## 4.3 Patient Identification

Patients will be defined by their unique, seven-digit identification number assigned at screening of the Parent Study (see Section 4.4 of the Parent Study).

## 5 STUDY DRUG – EXTENSION STUDY

### 5.1 Identity

**Product:** N-Acetyl-L-Leucine (internal development name: IB1001)

**Chemical name:** 2(S)-(acetylamino)-4-methylpentanoic acid

**Generic name:** N-Acetyl-L-Leucine

**Trade name:** to be determined

Two IMPs of equal strength and comparable dosage forms may be used during the Extension Phase:

1. The original IMP approved for use in the Parent Study ("Powder for oral suspension", packed in 60 mL glass bottles, see Section 5.1.1) or;
2. The commercial formulation developed for use in the Extension Phase ("Granules for oral suspension in sachet", see Section 5.1.2)

Information on both IMPs is provided below.

#### *5.1.1 N-Acetyl-L-Leucine, 1000 mg powder for oral suspension in 60 mL glass bottles (without further excipients)*

**Strength:** 1000 mg per 60 mL glass bottle

**Manufacturer:**

Manufacture of dosage form, QC testing, Stability studies:

[redacted]

Secondary packaging, Labelling, IMP release, Clinical distribution

[redacted]

**Description:**

[redacted]

[redacted]

**Preparation before administration:**

[redacted]

### *5.1.2 N-Acetyl-L-Leucine, [redacted] Granules for oral suspension in sachet*

**Strength:** [redacted]

**Manufacturer:**

Manufacture of dosage form, QC testing, Stability studies:

[redacted]

Secondary packaging, Labelling, IMP release, Clinical distribution

[redacted]

**Description:**

The product is formulated as 1000 mg granules for oral suspension in sachet.

[redacted]

**Preparation before administration:**

[redacted]

## 5.2 Administration

All patients are to receive N-Acetyl-L-Leucine (IB1001).

See Section 5.1.1 and Section 5.1.2 for instructions regarding preparation before administration for the powder for oral suspension and the granules for oral suspension, respectively.

[redacted]

During the treatment period of this Extension Phase, the dosing of the study drug is as follows:

- Patients aged ≥13 years will take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing 15 to <25 kg will take 2 g per day: 1 g in the morning and 1 g in the evening.
- Patients aged 6-12 years weighing 25 to <35 kg will take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Patients aged 6-12 years weighing ≥35 kg will take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening (as per patients aged ≥13).

Study drug will be taken during the two 365-day (+/- 14 days) treatment periods. The patient's dose for the extension treatment phase will be determined based on their age and weight at **Visit 7**. In the event a patient turns 13 years old or a patient aged 6-12 years old changes weight categories between **Visit 7** and **Visit 8** of the Extension Phase, their daily dose will be adjusted accordingly at **Visit 8.** In the event a patient turns 13 years old or a patient aged 6-12 years old changes weight categories between **Visit 8** and **Visit 10, or Visit 10 and Visit 11 of the** Extension Phase, their daily dose will be adjusted accordingly at **Visit 10 or Visit 11.**

## 5.3 Modification of Dose Schedule and Transition to Sachet Formulation

### *5.3.1 Modification of Dose*

On visit days, patients should keep to their usual dosing schedule, except for Visit 9B, which is a PK day.

If a patient misses a dose of study drug, the patient should wait and take the next dose according to the treatment schedule.

Compliance will be assessed upon a review of the inventory of IB1001 bottles/sachets returned by patients.

The patient's total daily dose may be reduced by up to one-half of their assigned dose at the discretion of the investigator.

At Visit 8, Visit 10, or Visit 11, the patient's daily dose may be modified if a patient aged 6-12 years turned 13 or if a patient aged 6-12 years changed weight category since the previous visit (see Section 5.2).

During the Extension Phase treatment period I, study drug will be taken for 365 days (+/- 14 days). After the 365-day (+/- 14 days) extension phase treatment period I, patients will enter a 42-day (+14 days) extension phase washout period, which includes efficacy and safety assessments. During the Extension Phase treatment period II (starting at the end of the extension phase washout), study drug will then be taken for an additional 365 days (+/- 14 days).

See Section 5.9 for information on the treatment of overdose.

### *5.3.2 Transition from IB1001 in Bottles to Sachet Formulation*

It is planned that all patients will receive the sachet formulation for the duration of the Extension Phase treatment period (see Section 5.1.2).

Patients may receive IB1001 in bottles at the beginning of the Extension Phase treatment period depending on the availability of the sachet supply (see Section 5.1.1). In this event, patients will transition to the sachet formulation at the instruction of the Investigator during the Extension Phase. To receive the sachet formulation, patients should visit the study site for an unscheduled visit to be trained on how to administer the sachet formulation. At this visit, all used, partially used, or unused kits (IB1001 bottles and Ora-Blend® bottles) should be returned to the study site[43].

Due to the outbreak of COVID-19, there is a great need to minimize immediate risks and prioritize the safeguarding of patients, their families, and clinical study teams by minimizing all potential exposure to COVID-19.

Accordingly, if necessary, instead of attending the study site for this unscheduled visit, patients may be trained remotely on how to prepare the sachet formulation. In this event, the addendum to the informed consent regarding the sachet formulation may also be performed remotely.

## 5.4 Packaging, Labeling and Storage

The IB1001 bottle and sachet formulations will be packaged by [redacted] or by [redacted] according to all local legal requirements. Study drug will be labelled in accordance with applicable regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

Packaging and labelling of IMP will comply with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) rules, EU GMP Annex 13, and country-specific regulatory requirements. Packaging and labeling of the IMP will be available in the local language.

### *5.4.1 N-Acetyl-L-Leucine, 1000 mg powder for oral suspension in 60 mL glass bottles (without further excipients)*

[redacted]

[43] Or after the Visit if IMP is returned via courier

#### 5.4.2 *N-Acetyl-L-Leucine, 1000 mg granules for oral suspension in sachet*

[redacted]

### 5.5 Blinding and Breaking the Blind

This study is not blinded. Videos collected from each study visit (except Visit 0 or unscheduled visits) and associated pairs of videos will be assessed in a blinded way by the independent raters.

### 5.6 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study. Study drug accountability will be performed at Visit 8 and Visit 9 and, if applicable, at the Extension Phase early termination visit. Unused or returned drug will be destroyed at the site. Alternatively, the study drug may be returned to [redacted] if the study drug cannot be destroyed at the site. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for maintaining up to date inventory and site accountability logs. Each dispensing of study drug to a patient will be documented in the medical records and patient-level accountability logs.

### 5.7 Investigational Medicinal Product (IMP; 'study drug') Compliance

At Visit 8 and Visit 11[45] patients should return all used IB1001 materials (IB1001 bottles, sachets, Ora-Blend® bottles).

At Visit 9, Visit 12, or Early Termination (if applicable), patients should return all study materials (i.e. used and unused IB1001 bottles and sachets and used and unused Ora-Blend® bottles [if applicable]) to the trial site for compliance checks.

Compliance will be assessed upon a review of the inventory of IB1001 bottles/sachets returned from patients.

### 5.8 Concomitant Medications and Therapies

All medication taken after Visit 6 will continue to be recorded as concomitant medications. The current amount (in hours per week) of therapy (e.g. physiotherapy, speech therapy) needs to continue to be recorded.

Table 5.1 lists medications that are prohibited. Medication not listed in this table may be permitted, at the discretion of the investigator, as long as there is no interference

[44] Labels based on assumption of a total daily dose of 4 g/day.
[45] If an unscheduled visit occurs during the extension phase treatment period, where patients switch from taking the IB1001 bottles to the IB1001 sachets, all used, partially used, or unused IB1001 kits (IB1001 bottles + Ora-Blend bottles) must be returned at this visit, or after the visit if the IMP is returned via courier.

with the study objectives or patient safety. Doses of medications and therapies used for (the symptoms of) NPC should remain as constant as possible (at the investigator's discretion) throughout the trial.

**Table 5.1: Prohibited Medications**

| |
|---|
| Aminopyridines (including sustained-release form) |
| N-Acetyl-DL-Leucine (e.g. Tanganil®) or N-Acetyl-L-Leucine (if not provided as study drug during the study) |
| Riluzole |
| Gabapentin |
| Varenicline |
| Chlorzoxazone |
| Sulfasalazine |
| Rosuvastatin |

Any medication the patient takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the electronic case report form (eCRF). The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

A patient found using a new concomitant medication, or a patient who changes their previous regimen/dose, may continue with the study/study drug if the Investigator does not believe the medication/therapy will interfere with the patient's safety.

[redacted]

### 5.9 Treatment of Overdose

No specific information on overdose of N-Acetyl-L-Leucine (IB1001) exists for humans. Based on the pharmacology, it is not expected that overdose would produce a clinically relevant reaction. The patient should be appropriately monitored.

# 6 PARAMETERS AND METHODS OF ASSESSMENT – EXTENSION PHASE

All analyses of the extension phase are considered secondary to ones of the parent study. For the most part, the same clinical outcome assessments used during the Parent Study (described in Section 6 of the Parent Study) will be used during the Extension Phase. These outcome assessments will be used in the Extension Phase to continue to monitor the long-term effects of IB1001. The section below describes how existing efficacy parameters have been updated for use in the Extension Phase, as well as additional efficacy parameters that have been added. Assessments in the Extension Phase will be performed at the times indicated in the Extension Phase schedule of events (see Table 6.1).

## 6.1 Updated Efficacy Parameters

### *6.1.1 Measurement of Global Impression*

The clinical global impression of severity (CGI-S) and change (CGI-C) will continue to be measured, with the questions for the physicians, caregivers, and patients modified to accommodate the Extension Phase visits.

Physician, Caregivers, and Patients (if able) will be asked to assess the CGI-S at each visit (Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12 and at the Extension Phase Early Termination visit, if applicable). The question is identical to that described in the Parent Study Section 6.1.5.

Physician, Caregivers, and Patients (if able) will be asked to assess the CGI-C at Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and the Extension Phase Early Termination Visit (if applicable).

**The Clinical Global Impression of Change (CGI-C) - clinician asks the clinician one question:**

*"Compared to the patient's condition at:*

*(i) Visit 7 (extension phase baseline) versus (ii) Visit 8 (interim extension phase treatment visit) OR versus Visit 9 (end of extension phase treatment);*

*OR*

*(i) Visit 9 (end of extension phase treatment) versus (ii) Visit 10 (end of extension phase washout);*

*OR*

*(i) Visit 10 (end of extension phase washout) versus (ii) Visit 11 (interim extension phase treatment visit) OR versus Visit 12 (end of extension phase treatment period II);*

*OR*

*(i) Early Termination Visit versus (ii) the previous visit,*

*this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse."*

**The Clinical Global Impression of Change (CGI-C) - caregiver asks the caregiver one question:**

*"Compared to the patient's condition at:*

*(i) Visit 7 (extension phase baseline) versus (ii) Visit 8 (interim extension phase treatment visit) OR versus Visit 9 (end of extension phase treatment);*

*OR*

*(i) Visit 9 (end of extension phase treatment) versus (ii) Visit 10 (end of extension phase washout);*

*OR*

*(i) Visit 10 (end of extension phase washout) versus (ii) Visit 11 (interim extension phase treatment visit) OR versus Visit 12 (end of extension phase treatment period II);*

*OR*

*(i) Early Termination Visit versus (ii) the previous visit,*

*how much has he/she changed: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse."*

**The Clinical Global Impression of Change (CGI-C) - patient asks the patient (*if able*) one question:**

*"Compared to your condition at:*

*(i) Visit 7 (extension phase baseline) versus (ii) Visit 8 (interim extension phase treatment visit) OR versus Visit 9 (end of extension phase treatment);*

*OR*

*(i) Visit 9 (end of extension phase treatment) versus (ii) Visit 10 (end of extension phase washout);*

*OR*

*(i) Visit 10 (end of extension phase washout) versus (ii) Visit 11 (interim extension phase treatment visit) OR versus Visit 12 (end of Extension Phase Treatment Period II);*

*OR*

*(i) Early Termination Visit versus (ii) the previous visit,*

*how much have you changed? 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse."*

#### *6.1.2 Clinical Impression of Change in Severity*

Videos of the primary and non-primary anchor tests are collected throughout the extension phase for the Clinical Impression of Change in Severity (CI-CS). These videos may be analyzed in order to inform the development and validation of the CI-CS endpoint.

## 6.2 New Efficacy Parameters Introduced for the Extension Phase

### *6.2.1 NPC Clinical Severity Scale (NPC-CSS)*

The NPC clinical severity scale (NPC-CSS) [Yanjanin et al, 2010] was developed and validated in a cross-sectional study of current NPC patients and a longitudinal chart review of an historical cohort. The scale quantifies the major symptoms of NPC and characterizes the disease progression of NPC. The NPC-CSS measures clinical signs and symptoms in 9 major (ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, swallowing) and 8 minor (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory problems) domains. A higher NPC-CSS score indicates a clinical worsening, while a lower NPC-CSS score indicates a clinical improvement. A 0-point change in the NPC-CSS score represents a stabilization of disease progression, which is also a significant clinical improvement for rapidly progressive, neurogenerative diseases like NPC.

NPC-CSS is a widely accepted clinical outcome measure for NPC trials that investigate long-term treatment effect. Several clinical trials in patients with NPC have change in NPC-CSS as primary endpoint, including a Phase IIb/III clinical trial of 2-hydroxypropyl-β-cyclodextrin (VTS-270; ClinicalTrials.gov ID: NCT02534844), a Phase II/III clinical trial of arimoclomol (NCT02612129), and an open-label Phase I/II clinical trial of lithium carbonate (NCT03201627).

A recent consensus paper on clinical management guidelines for Niemann-Pick disease type C recommended that, bearing in mind the resources available to most physicians in practice, a modified version of the NPC-CSS that is widely used in clinical practice, and more user-friendly, should be administered. This modified version excludes the hearing and auditory brainstem response domains [Geberhiwot et al, 2018]. Accordingly, all major and minor domains of the NPC-CSS [Yanjanin et al, 2010] will be assessed in this study, with the exception of the hearing and auditory brainstem response domains. The change in the full NPC-CSS score, apart from hearing domains (i.e. hearing and auditory brainstem response), will be calculated.

It is also planned that a stratified version of the NPC-CSS scale, limited to the assessment of 5 NPC-CSS domains (Ambulation, Cognition, Fine motor, Speech, and Swallowing) will also be evaluated (this is a primary endpoint in the arimoclomol trial; NCT02612129) as the primary objective in the extension phase.

If an NPC-CSS score is available from Visit 1 of the Parent Study, additional analysis will be performed comparing the NPC-CSS at Visit 1, Visit 7, Visit 9, and Visit 10.

Finally, while providing informed consent for participation Extension Phase, patients (or their legal representative on their behalf) will be asked if they agree to provide relevant medical history, including outcomes of NPC-CSS assessments conducted prior to their enrollment and participation in the Parent Study. Provided the patient (or legal representative on their behalf) consents, the available retrospective data may be used to conduct additional analyses which assess the slope of disease progression before

enrollment in the trial and after the initiation of treatment with IB1001. The same investigator should perform the NPC-CSS at all extension phase Visits (Visit 7 – Visit 12).[46]

#### *6.2.2 Annual Severity Increment Score (ASIS)*

The Annual Severity Increment Score (ASIS) [Cortina-Borja et al, 2018] is a metric that measures the annual increment in clinical severity for individual NPC patients. The ASIS score is based on the assessments performed in the NPC-CSS assessment; no additional tests are required. The ASIS score is obtained by dividing the total NPC-CSS severity score of a patient by the age of the patient, providing a measure of the rate of disease progression in individual patients.

Cortina-Borja et al (2018) demonstrated in 38 patients from two independent international clinical cohorts that the ASIS was stable over several years. They also applied the ASIS score to quantify the slowing of the rate of disease progression in 10 NPC patients receiving long-term treatment with Acetyl-DL-Leucine. The study demonstrated that the ASIS is a reliable predictor of progression of clinical severity and a valuable tool to quantify the effect of an experimental therapy for NPC disease progression.

The ASIS scale is included to quantify the potential effects of IB1001 as a neuroprotective/disease-modifying treatment for NPC.

### 6.3 Exploratory Endpoints for the Washout Phase

Exploratory endpoints are defined in Section 8.5.2.

### 6.4 Safety Parameters

The Investigator is responsible for monitoring the safety of patients who have been enrolled in this study and for accurately documenting and reporting information as described in this section.

#### *6.4.1 Adverse Events*

See Section 6.2.1 of the Parent Study.

#### *6.4.2 Serious Adverse Events*

See Section 6.2.2 of the Parent Study.

#### *6.4.3 Pregnancy*

The policies for pregnancy are identical to the Parent Study (see Section 6.2.3 of the Parent Study) except that at all visits of the Extension Phase (Visits 7 through Visit 10 and the Extension Phase Early Termination Visit [if applicable]), females of childbearing potential will have a urine dipstick pregnancy test (analyzed on site).

[46] In addition, the same investigator should perform the SARA assessment at all extension phase Visits (Visit 7 – Visit 12)

#### *6.4.4 Vital Signs*

Vital signs will be measured and recorded at the time points designated on the Extension Phase schedule of events (see Table 6.1), in accordance with the procedures and policies described in Section 6.2.4 of the Parent Study.

#### *6.4.5 Electrocardiograms (ECGs)*

During the Extension Phase, one 12-lead ECG will be performed at the time point designated on the Extension Phase schedule of events (Table 6.1), following the procedures and policies provided in Section 6.2.5 of the Parent Study.

In addition, ECGs may be performed at other visits at the discretion of the Investigator.

#### 6.4.6 *Physical Examinations*

A complete physical examination that is limited to the following body systems: general appearance (including skin), head and neck, eyes and ears, nose and throat, pulmonary, cardiovascular, gastrointestinal, muscular skeletal, lymphatic, neurological, will be performed at the time points designated on the Extension Phase schedule of events (Table 6.1).

If a new, significant abnormal or worsened abnormal pre-existing condition is detected, the condition needs to be recorded as an AE.

Weight will be measured at the time points designated on the Extension Phase schedule of events (Table 6.1).

#### *6.4.7 Medical History*

While providing informed consent for participation Extension Phase, patients (or their legal representative on their behalf) will be asked if they agree to provide relevant medical history, including outcomes of NPC-CSS assessments conducted prior to their enrollment and participation in the Parent Study. Provided the patient (or legal representative on their behalf) consents, the available retrospective data may be used to conduct additional analyses which assess the slope of disease progression before enrollment in the trial and after the initiation of treatment with IB1001.

### 6.5 Laboratory Parameters

#### *6.5.1 Safety Laboratory Assessments*

Samples will be collected and analyzed by standard laboratory procedures at the time points designated on the schedule of events – Extension Phase (see Table 6.1), in accordance with the procedures and policies described in Section 6.3.1 of the Parent Study.

The total amount of blood taken per patient during the study (Parent Study + Extension Phase) is provided in Section 6.5.5.

#### *6.5.2 Measurement of N-Acetyl-L-Leucine Concentration in Blood on FULL PK days*

Blood samples for the quantification of N-Acetyl-L-Leucine in plasma will be obtained according to the Extension Phase schedule of events (Table 6.1).

At **Visit 7B,** the first sample will be taken before first dosing of N-Acetyl-L-Leucine in the Extension Phase; subsequent samples will be taken at 30 minutes (+/- 5 minutes), 60 minutes (+/- 5 minutes), 90 minutes (+/- 10 minutes), 120 minutes (+/- 10 minutes), 150 (+/- 15 minutes), 180 minutes (+/- 15 minutes), 240 minutes (+/- 15 minutes), and 360 minutes (+/- 15 minutes) after the first extension phase IMP dose is taken.

At **Visit 9B**, the first sample will be taken directly before last IMP intake of the treatment period; subsequent samples will be taken at 30 minutes (+/- 5 minutes), 60 minutes (+/- 5 minutes), 90 minutes (+/- 10 minutes), 120 minutes (+/- 10 minutes), 150 minutes (+/- 15 minutes), 180 minutes (+/- 15 minutes), 240 minutes (+/- 15 minutes), and 360 minutes (+/- 15 minutes) after the last extension phase IMP dose is taken.

At Visit 7B and Visit 9B, it is important that the day and exact time of the dose of N-Acetyl-L-Leucine that is taken after the first pre-dose PK blood draw, and before the subsequent first post-dose blood draw at 30 minutes (+/- 5 minutes) is recorded.

At Visit 7B and Visit 9B, for each PK blood draw, it is important that the day and exact time of each blood draw is recorded.

On Visit 7B and Visit 9B, when full PK sampling is conducted, the drug should be taken in accordance with the protocol (that is, taken 30 minutes before or at least two hours after a meal). In addition, on Visit 7B and Visit 9B, the days PK sampling is conducted, all meal times should be recorded until the last PK draw has been made. For Visit 7, the next dose of N-Acetyl-L-Leucine should be taken after the last PK draw has been made at the earliest. Note, for Visit 9B, no further doses will be given after the PK draws until the end of Visit 10 (Visit 9B marks the end of the Extension Phase treatment period I). Shipment instructions for N-Acetyl-L-Leucine PK blood samples will be provided in the laboratory manual.

The total amount of blood taken per patient during the Extension Phase (that is, in addition to the Parent Study) is provided in Section 6.5.5.

#### *6.5.3 Measurement of N-Acetyl-D-Leucine Concentration in Urine*

Urine tests for N-Acetyl-D-Leucine will be done pre-dose at Visit 7A[47], and pre-dose at Visit 10. Data will be analyzed in batches and used for sensitivity analyses only.

#### *6.5.4 Additional Laboratory Samples for Research Purposes*

Retained samples from the Parent Study or Extension Phase may be used for research purposes to provide more information on the disease NPC.

Blood samples will be obtained for possible research purposes to provide more information on the disease NPC according to the Extension Phase schedule of events (Table 6.1).

#### *6.5.5 Total Blood Volume*

The total amount of blood taken per subject during the Extension Phase will be approximately 119 mL (35 mL for safety analysis, and 72 mL for the PK analysis, 12 mL for research purposes). If a safety laboratory analysis is performed at Visit 7, Part

[47] If Visit 7 is scheduled within +7 days of Visit 6, the urine test for N-Acetyl-D-Leucine taken at Visit 6 may be used as the pre-dose urine test.

A, an additional 7 mL will be taken, and the total amount of blood taken per subject during the Extension Phase will be approximately 126 mL.

The total of blood taken during the total study, Parent study + Extension phase, will be approximately 192 mL (66 mL from the Parent study + 126 mL from the Extension Phase).

# 7 STUDY CONDUCT – EXTENSION PHASE

## 7.1 Observations by Visit

### *7.1.1 Visit 7: Extension Phase Baseline Visit*

**Visit 7:** The assessments comprising Visit 7 may be conducted over a two-day period ("Part A" and "Part B")[48]. If Visit 7, Part B is scheduled 1 day (+6 days) after Visit 6 (Washout 2), the assessments defined as Part A will use the results obtained at Visit 6.

At **Visit 6** of the Parent Study, the PI should determine continued treatment with IB1001 to be in the patient's best interest, and, provided the patient/caregiver would like to continue participation in the Extension Phase, the PI should obtain informed consent/informed consent form (ICF) signature and patient information (see Section 7.1.6 of the Parent Study).

**Visit 7, Part A**: Part A of the Extension Phase baseline assessment.

If Visit 7, Part B is scheduled 1 day (+6 days) after Visit 6, the results obtained for assessments at Visit 6 can be carried over to Visit 7, Part A (i.e. assessments performed at Visit 6 don't need to be repeated). If Visit 7, Part B cannot be scheduled within 1 day (+6 days) after Visit 6, Visit 7 Part A assessments must be carried out and Visit 7 may be conducted over 2 days.

- Addendum to the informed consent/informed consent form (ICF) signature and patient information for Extension Phase (if applicable)
- Check of inclusion/exclusion criteria for Extension Phase (if applicable)
- Vital signs
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient if able
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine
- Blood draw for laboratory safety tests (done at central lab)
- Blood draw for research purposes
- Documentation of adverse events.

[48] If Visit 7 is conducted within +7 days of Visit 6, the assessments performed at "Visit 7 Part A" do not need to be duplicated.

***Visit 7, Part B:*** Part B of the Extension Phase baseline assessment. Scheduled either 1 day (+6 days) after Visit 6, or +1 Day after Visit 7, Part A. Start of IMP during the Extension Phase.

- Physical examination
- Weight
- Niemann-Pick Disease Type C Clinical Severity Scale (NPC-CSS)
- Pre-dose blood draw for PK (taken directly before the first dose of N-Acetyl-L-Leucine in the Extension Phase) (done at PK lab)
- Dispensing of study drug + intake of study drug at site
- Blood draws for PK taken at the defined post-dose timepoints (done at PK lab)
- Documentation of adverse events.

#### *7.1.2 Visit 8: Day 180 (+/- 14 days): First assessment of the Extension Phase treatment period I with N-Acetyl-L-Leucine*

- Return of trial drug and compliance check
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick disease type C Clinical Severity Scale
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on Visit 7
- Clinical Global Impression of Change (CGI-C) by caregiver based on Visit 7
- Clinical Global Impression of Change (CGI-C) by patient *if able* based Visit 7
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Blood draw for safety laboratory tests (done at central lab)
- Documentation of adverse events
- Dispensing of additional study drug.

#### *7.1.3 Visit 9: Day 365 (+/- 14 days): Final assessments of the Extension Phase treatment period I with N-Acetyl-L-Leucine*

The assessments comprising Visit 9 may be conducted over a two-day period ("Part A" and "Part B").

*7.1.3.1 Visit 9, Part A: Day 365 (+/- 14 days) of the treatment period*

- Spinocerebellar Ataxia Functional Index (SCAFI) + including Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick Disease Type C Clinical Severity Scale (NPC-CSS)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on Visit 7
- Clinical Global Impression of Change (CGI-C) by caregiver based on Visit 7
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on Visit 7
- 12-lead ECG
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Documentation of adverse events.

*7.1.3.2 Visit 9, Part B*

The final treatment visit in the Extension Phase. +1 Day after Visit 9, Part A.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for research purposes
- Pre-dose blood draw for PK (taken directly before the last dose of N-Acetyl-L-Leucine in the Extension Phase) (done at PK lab)
- Last intake of study drug at site
- Blood draws for PK taken at the defined post-dose timepoints (done at PK lab)
- Return of trial drug and compliance check
- Documentation of adverse events.

### *7.1.4 Visit 10: Extension Phase Washout Visit*

The final day/first assessment of Extension Phase washout period.

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick Disease Type C Clinical Severity Scale (NPC-CSS)

- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on previous visit
- Clinical Global Impression of Change (CGI-C) by caregiver based on previous visit
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on previous visit
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Documentation of adverse events
- Addendum to the informed consent/informed consent form (ICF) signature and patient information for Extension Phase treatment period II (if applicable)
- Dispensing of study drug + intake of study drug at site.

#### *7.1.5 Visit 11: Day 587 (+/- 14 days): Interim Extension Phase visit treatment period II*

- Return of trial drug and compliance check
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick disease type C Clinical Severity Scale (NPC-CSS)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on Visit 10
- Clinical Global Impression of Change (CGI-C) by caregiver based on Visit 10
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on Visit 10
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Blood draw for safety laboratory tests (done at central lab)
- Documentation of adverse events
- Dispensing of additional study drug.

#### *7.1.6 Visit 12 Day 767: Final assessments of the Extension Phase treatment period II with N-Acetyl-L-Leucine*

- Return of trial drug and compliance check

- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick disease type C Clinical Severity Scale (NPC-CSS)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on Visit 10
- Clinical Global Impression of Change (CGI-C) by caregiver based on Visit 10
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on Visit 10
- Urinalysis (done at central lab)
- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for research purposes
- Documentation of adverse events.

#### *7.1.7 Extension Phase Early Termination (ET)*

- Return of trial drug and compliance check
- Documentation of frequency of therapy (hours per week)
- Documentation of concomitant medication
- Vital signs
- Physical examination
- Weight
- Spinocerebellar Ataxia Functional Index (SCAFI) + Video-Recording of Clinical Impression of Change in Severity (CI-CS) Anchor Tests (9HPT-D and 8MWT)
- Scale for Assessment and Rating of Ataxia (SARA)
- Niemann-Pick Disease Type C Clinical Severity Scale (NPC-CSS)
- Quality of Life EQ-5D-5L for patients aged ≥18 years, EQ-5D-Y for patients aged <18 years
- Clinical Global Impression of Severity (CGI-S) by physician
- Clinical Global Impression of Severity (CGI-S) by caregiver
- Clinical Global Impression of Severity (CGI-S) by patient *if able*
- Clinical Global Impression of Change (CGI-C) by physician based on previous visit
- Clinical Global Impression of Change (CGI-C) by caregiver based on previous visit
- Clinical Global Impression of Change (CGI-C) by patient *if able* based on previous visit
- 12-lead ECG
- Urinalysis (done at central lab)

- Urine by dipstick: pregnancy test for women of childbearing potential (done at site)
- Urine test for N-Acetyl-D-Leucine (done at PK lab)
- Blood draw for safety laboratory tests (done at central lab)
- Blood draw for research purposes
- Documentation of adverse events.

# 8 STATISTICAL METHODS – EXTENSION PHASE

## 8.1 General Analysis Plan

### *8.1.1 Disposition of Patients*

The number of patients enrolled, plus the numbers contained within the Extension Phase Safety Analysis Set (SAFe), intention-to-treat (ITTe), modified intention-to-treat analysis set (mITTe), and the Per Protocol Set (PPSe) will be summarized overall and by country. The number of patients discontinuing treatment, together with the primary reason for discontinuation will be presented.

*Protocol Deviations*

Protocol deviations include but are not limited to:

- Violation of key inclusion /exclusion criteria
- Use of Prohibited Medications

Further detail will be provided in the Statistical Analysis Plan (SAP)

### *8.1.2 Analysis Populations*

- The Safety Analysis Set Extension Phase (SAFe) will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine) in the Extension Phase
- The intention-to-treat Extension Phase (ITTe) population will consist of all patients who receive at least one dose of study drug (N-Acetyl-L-Leucine) in the Extension Phase and with NPC-CSS scores at baseline (Visit 7)
- The extension phase modified intention to treat analysis set (mITTe) will consist of all patients with NPC-CSS scores at baseline (Visit 7) and end of treatment period I (Visit 9).
- The Per Protocol Set Extension Phase (PPSe) will consist of all patients with NPC-CSS scores at baseline (Visit 7) and end of treatment period I (Visit 9) without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variable

## 8.2 General Considerations

Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

All variables will be summarized using descriptive statistics. The number of patients, mean, standard deviation (SD), minimum, median, and maximum will be calculated for continuous and score variables. Frequency tables will be generated for categorical data.

90% confidence intervals, together with a one-sided significance level of 0.05 where appropriate, will be used for all endpoints as a guide for evidence for activity. Conclusions regarding treatment efficacy will not solely rely on detecting statistical significance with equal emphasis placed on the magnitude and clinical relevance of treatment differences as judged by the point estimates and confidence intervals.

No correction for multiple comparisons will be included.

## 8.3 Demographics, Baseline Characteristics and Concomitant Medications

Demographic data and patient characteristics at baseline will be summarized descriptively.

Frequency and percentage of prior and concomitant medication use will be summarized by World Health Organization (WHO) Drug dictionary coded terms - Anatomic Therapeutic Chemical (ATC) classification and preferred term.

## 8.4 Treatment Compliance

Summary statistics for the number of N-Acetyl-L-Leucine doses taken, based on bottles or sachets of Study Drug dispensed and return bottle or sachet counts, will be calculated. Overall compliance in terms of the percentage of drug taken based on these data will be summarized descriptively together with the proportion of patients who take at least 80% of the prescribed medication.

## 8.5 Efficacy Analyses

The primary analyses of efficacy will be based on the mITTe analyses of efficacy based on the PPSe will also be undertaken to provide supplementary information.

For the primary endpoint there will be separate analyses within key subgroups. The subgroups to be considered will be defined by:

- Naïve versus non-naïve: trial classification as determined at screening
- Patients on miglustat versus patients not on miglustat
- Age (pediatric versus adult)
- Age/weight/dosing group
- Age of diagnosis: Early-infantile (<2 years), Late-infantile (2 to < 6 years), Juvenile (6 to < 15 years), Adolescent/Adult (≥ 15 years)
- Disease severity based on NPC-CSS below/ above the median NPC-CSS score at Visit 7
- Gender (male versus female)
- Primary Anchor Test (9HPT-D or 8MWT)
- Composite of SARA Subtests 1-4 (Gait, Stance, Sitting, Speech)
- Composite of Modified NPC-CSS score: Ambulation, Cognition, Fine motor, Speech and Swallowing
- Stratification based on Annual Severity Increment Score (ASIS)

Additional subgroups can be added at the time of analysis on an exploratory basis.

Separate Extension Phases are planned to be conducted with N-Acetyl-L-Leucine for NPC, GM2-gangliosidosis, and ataxia-telangiectasia. There will however be a planned series of meta-analyses that will bring together the data from the studies for the primary and selected exploratory endpoints. Further details will be provided in a meta-analysis statistical analysis plan (MASAP).

### *8.5.1 Primary Efficacy Endpoint*

The primary endpoint is based on the modified 5-domain NPC-CSS score with success defined as no change or a decrease in the 5-domain NPC-CSS score from Visit 7 to Visit 9.

It is postulated that under standard of care, 90% of patients would worsen (higher score) in terms of their performance in 5-domain NPCS-CSS scale over a 12-month period, while conversely only 10% would show similar performance or some improvement. Statistical evaluation of the primary binary endpoint (success/failure on the 5-Domain

NPC-CSS scale) will compare the proportion of success with 10% in a one-sided Fishers Exact test at the one-sided 5% significance level.

### *8.5.2 Exploratory Efficacy Endpoints*

Additional exploratory endpoints will investigate other measures of symptoms and quality of life. Descriptive statistics will be provided for these measures at each visit and also changes from Extension Phase baseline (Visit 7) to the end of Extension Phase treatment period I with N-Acetyl-L-Leucine (Visit 9) for the following measures:

- Spinocerebellar Ataxia Functional Index (SCAFI)[49] score
- Scale for Assessment and Rating of Ataxia (SARA) score
- Niemann-Pick Disease Type C Clinical Severity Scale (NPC-CSS)
- Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y[50] for patients aged <18 years
- Treating Physician Clinical Global Impression of Severity (CGI-S)
- Treating Physician Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 9) to Extension Phase baseline (Visit 7)
- Caregiver Clinical Global Impression of Severity (CGI-S)
- Caregiver Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 9) to Extension Phase baseline (Visit 7)
- Patient Clinical Global Impression Scales Impression of Severity (CGI-S) *if they are able*
- Patient Clinical Global Impression of Change (CGI-C) comparing end of treatment (Visit 9) to Extension Phase baseline (Visit 7) *if they are able*
- Annual Severity Increment Score (ASIS)

Videos of the primary and non-primary anchor tests are collected throughout the extension phase for the CI-CS. These videos may be analyzed in order to inform the development and validation of the CI-CS.

#### *8.5.2.1 Exploratory Efficacy Endpoints related to the Washout Phase*

Exploratory endpoints in the Extension Phase may also be based on changes over the following time periods:

- The beginning of the Extension Phase (Visit 7) to the end of the Extension Phase washout period (Visit 10)
- The end of the Extension Phase treatment period I (Visit 9) to the end of the Extension Phase washout period (Visit 10).
- The end of Extension Phase period I washout (Visit 10) to the end of Extension Phase treatment period II (Visit 12)
- The beginning of the Parent study (Visit 1) to the end of the Extension Phase treatment period II (Visit 12)

[49]The 9 Hole Peg Test of the Dominant Hand (9HPT-D) and the 8 Meter Walk Test (8MWT) will be videoed for every patient at every visit except Visit 0 of the parent study.
[50] European Sites Only

Finally, exploratory endpoints will be based on the changes on the Niemann-Pick Disease type C Clinical Severity Scale (NPC-CSS) and the five-domain NPC-CSS scale. An exploratory evaluation of the NPC-CSS will be based on the changes from Extension Phase baseline (Visit 7) to the end of the Extension Phase washout period (Visit 10).

If a NPC-CSS score is available from Visit 1 of the Parent Study, additional analysis will be performed comparing the NPC-CSS at Visit 1, Visit 7, Visit 9, Visit 10, Visit 11, and Visit 12.

While providing informed consent for participation Extension Phase, patients (or their legal representative on their behalf) will be asked if they agree to provide relevant medical history, including outcomes of NPC-CSS assessments conducted prior to their enrollment and participation in the Parent Study. Provided the patient (or legal representative on their behalf) consents, the available retrospective data may be used to conduct additional analyses which assess the slope of disease progression before enrollment in the trial and after the initiation of treatment with IB1001.

All exploratory endpoints relating to the washout phase, or the Extension Phase Treatment period II, will be evaluated based on descriptive statistics.

### 8.6 Missing Data

Analyses based on the mITTe analysis set will utilize a last observation carried forward (LOCF) approach for a missing video at Visit 9.

For the primary endpoint 5-Domain NPC-CSS endpoint this implies that the score of Visit 8 will be used instead. Other endpoints will not be imputed, and missing data will be reported as is. No sensitivity analyses will be applied.

For all other endpoints there will be no imputation for missing data and data will be reported and evaluated as observed.

### 8.7 Blinding

This study is not blinded. Videos of the primary and non-primary anchor tests are collected throughout the extension phase for the CI-CS may be analyzed in order to inform the development and validation of the CI-CS. The blinded independent raters will be given each of the 3 videos initially in a random order to make their evaluation of CI-S for each video. The blinded independent raters will then be provided with 3 pairs of video recordings blinded to information on the visits associated with these videos and their order and asked to provide a score for CI-CS for each pair. Further details regarding this blinding process will be detailed in the SAP.

### 8.8 Safety Analyses

The SAFe will be the basis for all analyses of safety and tolerability.

### 8.9 Interim Analyses

There will be an analysis of the primary and other endpoints relating to the Extension Phase once all patients have completed Visit 10.

### 8.10 Determination of Sample Size

Sample size is determined by the number of patients that move into this Extension Phase from the parent study. The expectation is that between 60% and 70% of patients will rollover into the extension period. With 20 out of 32 patients (62.5%) rolling over, the study will have 80% power to detect an improvement in the success rate to 31% compared to the null hypothesis value of 10%.

## 9 DATA HANDLING AND RECORD KEEPING – EXTENSION PHASE

See Section 9 of Parent Study.

## 10 QUALITY CONTROL AND QUALITY ASSURANCE – EXTENSION PHASE

See Section 10 of the Parent Study.

## 11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS – EXTENSION PHASE

See Section 11 of the Parent Study.

## 12 LIST OF REFERENCES – EXTENSION PHASE


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**Table 6.1 – Schedule of Events for the Extension Phase**

| Period in the Extension Phase (EP) | EP Baseline Period | | EP Treatment Period I | | | EP Wash-Out Period | EP Treatment Period II | | EP Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **1 Day** | **1 Year** | | | **6 Weeks** | **1 Year** | | **1 Day** |
| **Visit number** | **Visit 7A[i]** | **Visit 7B** | **Visit 8** | **Visit 9A** | **Visit 9B** | **Visit 10** | **Visit 11** | **Visit 12 / EOS** | **ET** |
| **Name of the Visit** | **EP Screening/Bsl** | **EP Baseline** | **EP Treatment 1** | **EP Treatment 2** | **EP Treatment 2** | **EP Washout 1** | **EP Treatment 4** | **EP Treatment 5** | **EP ET** |
| **Timeline (Days)** | *Day -1* | *Day 1, Start IMP* | *Day 180* | *Day 365* | *Day 366* | *Day 407* | *Day 587* | *Day 767* | *XX* |
| **Visit Window allowed** | *na* | *+6 day[ii]* | *+/- 14 days* | *+/- 14 days* | *na* | *+14 days* | *+/- 14 days* | *+/- 14 days* | *na* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient information and informed consent process | X | | | | | X | | | |
| Inclusion / exclusion criteria | X | | | | | | | | |
| Patient Weight | | X | X | | X | X | X | X | X |
| Physical Examination | | X | X | | X | X | X | X | X |
| Documentation of concomitant medication | X | | X | | X | X | X | X | X |
| Documentation of frequency of therapy (hours per week) | X | | X | | X | X | X | X | X |
| Vital signs | X | | X | | X | X | X | X | X |
| 12-lead electrocardiogram (ECG) | | | | X | | | | | X |
| Blood safety laboratory tests[iii] | X | | X | | X | X | X | X | X |
| Blood samples for research purposes | X | | | | X | | | X | X |
| PK Blood Sampling[iv] | | X | | | X | | | | |
| Urinalysis | X | | X | X | | X | X | X | X |
| Urine by dipstick for pregnancy test[v] | X | | X | X | | X | X | X | X |
| Urine test for N-Acetyl-D-Leucine | X | | | | | X | | | X |
| Quality of Life EQ-5D-5L for patients aged ≥18; EQ-5D-Y for children aged <18 years[vi] | X | | X | X | | X | X | X | X |
| Scale for Ataxia Rating (SARA) | X | | X | X | | X | X | X | X |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Scale for Spinocerebellar Ataxia Functional Index (SCAFI) | X | | X | X | | X | X | X | X |
| Video-Recording Primary Anchor Tests (8MWT + 9HPT-D) | X[vii] | | X | X | | X | X | X | X |

| Period in the Extension Phase (EP) | EP Baseline Period | | EP Treatment Period I | | | EP Wash-Out Period | EP Treatment Period II | | EP Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **1 Day** | **1 Year** | | | **6 Weeks** | **1 Year** | | **1 Day** |
| **Visit number** | **Visit 7A[i]** | **Visit 7B** | **Visit 8** | **Visit 9A** | **Visit 9B** | **Visit 10** | **Visit 11** | **Visit 12 / EOS** | **ET** |
| **Name of the Visit** | **EP Screening/Bsl** | **EP Baseline** | **EP Treatment 1** | **EP Treatment 2** | **EP Treatment 2** | **EP Washout 1** | **EP Treatment 4** | **EP Treatment 5** | **EP ET** |
| **Timeline (Days)** | *Day -1* | *Day 1, Start IMP* | *Day 180* | *Day 365* | *Day 366* | *Day 407* | *Day 587* | *Day 767* | *XX* |
| **Visit Window allowed** | *na* | *+6 day[ii]* | *+/- 14 days* | *+/- 14 days* | *na* | *+14 days* | *+/- 14 days* | *+/- 14 days* | *na* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Niemann-Pick Disease type C Clinical Severity Scale[viii] | X | X | X | X | | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Physician | X | X | X | X | | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Caregiver | X | | X | X | | X | X | X | X |
| Clinical Global Impression of Severity (CGI-S) by Patient | X | | X | X | | X | X | X | X |
| Clinical Global Impression of Change (CGI-C) by Physician | | | X | X | | X | X | X | X |
| Clinical Global Impression of Change (CGI-C) by Caregiver | | | X | X | | X | X | X | X |
| Clinical Global Impression of Change (CGI-C) by Patient | | | X | X | | X | X | X | X |
| Documentation of AEs | X | X | X | X | X | X | X | X | X |
| Dispensing of study drug | | X | X | | | X | X | | |
| Intake of study drug at site | | X | | | X | | | | |
| Return of study drug[ix] | | | X | | X | | X | X | X[x] |
| Study drug compliance check | | | X | | X | | X | X | X |

Abbreviations: EP = Extension Phase; na = not applicable.

[i] Visit 7A may be taken from Visit 6, provided Visit 7B is scheduled within 1 day (+6 days) of Visit 6

[ii] if Visit 7B cannot be scheduled 1 day (+6 days) after Visit 6, Visit 7A and Visit 7B should be conducted over a two-day period on two consecutive days, i.e. Visit 7B occurs +1 day after Visit 7A

[iii] Analyzed at central lab

[iv] Analyzed at PK lab

[v] Only for women of childbearing potential; done at site

[vi] If a patient turns 18 over the course of the study, they should continue to use the EQ-5D-Y

| Period in the Extension Phase (EP) | EP Baseline Period | | EP Treatment Period I | | | EP Wash-Out Period | EP Treatment Period II | | EP Early Term. |
|---|---|---|---|---|---|---|---|---|---|
| **Duration of the whole period** | **1 Day** | **1 Day** | **1 Year** | | | **6 Weeks** | **1 Year** | | **1 Day** |
| **Visit number** | **Visit 7A[i]** | **Visit 7B** | **Visit 8** | **Visit 9A** | **Visit 9B** | **Visit 10** | **Visit 11** | **Visit 12 / EOS** | **ET** |
| **Name of the Visit** | **EP Screening/Bsl** | **EP Baseline** | **EP Treatment 1** | **EP Treatment 2** | **EP Treatment 2** | **EP Washout 1** | **EP Treatment 4** | **EP Treatment 5** | **EP ET** |
| **Timeline (Days)** | *Day -1* | *Day 1, Start IMP* | *Day 180* | *Day 365* | *Day 366* | *Day 407* | *Day 587* | *Day 767* | *XX* |
| **Visit Window allowed** | *na* | *+6 day[ii]* | *+/- 14 days* | *+/- 14 days* | *na* | *+14 days* | *+/- 14 days* | *+/- 14 days* | *na* |

[vii] If Visit 7A is based on Visit 6 assessments, the video recordings from Visit 6 should be used

[viii] All major and minor domains should be assessed, with the exception of the hearing and auditory brainstem response domains

[ix] Or after visit if IMP is returned via courier

[x] If applicable

*General note: due to COVID-19, deviations from the schedule of visits and assessments may be necessary. Any changes to the schedule of visits/assessments should be discussed between the PI and Sponsor.*