

Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C (NPC): A Phase III, randomized, placebo-controlled, double-blind, crossover study

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This study has been transitioned to CTIS with ID 2023-510278-14-00 check the CTIS register for the current data. Primary Objective: In all jurisdictions except the United States (US), the primary objective is to evaluate the efficacy of N-Acetyl-L-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON53762

Source

ToetsingOnline

Brief title

Pivitol study with N Acety L Leucine in Nieman Pick type C

Condition

- Inborn errors of metabolism

Synonym

Hereditary metabolic disease, NPC

Research involving

Human

Sponsors and support

Primary sponsor: IntraBio Ltd

Source(s) of monetary or material Support: IntraBio Ltd

Intervention

Keyword: N-Acetyl-L-Leucine, Niemann Pick type C

Outcome measures

Primary outcome

Primary Endpoint:

In Europe and Australia, the primary endpoint is the Scale for the Assessment and Rating of Ataxia (SARA). SARA 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.

In the United States (US), the primary endpoint is the modified Scale for the Assessment and Rating of Ataxia (mSARA). The mSARA is a six-item clinical rating scale (range 0-30, where 0 is the best neurological status and 30 the worst).

The primary endpoint is defined as the total SARA / mSARA value at the end of Period I (Visit 4) versus the end of Period II (Visit 6).

Secondary outcome

Secondary Endpoints:

The following secondary assessments will be evaluated:

- Spinocerebellar Ataxia Functional Index (SCAFI)
- SARA (key secondary endpoint - US only)
- Quality of Life EQ-5D-5L for patients aged ≥ 18 ; EQ-5D-Y for children aged < 18 years

- Modified Disability Rating Scale (mDRS)
- Treating Physician*s, Caregiver*s (if applicable) and Patient*s (if able)

Clinical Global Impression of Improvement (CGI-I)

Exploratory Endpoints:

- Sparse PK sampling will be collected to characterize the PK of

N-Acetyl-L-Leucine in patients with NPC

- Modified SARA (Europe/ Australia only)
- Niemann-Pick disease type C Clinical Severity Scale (NPC-CSS)
- 5-domain NPC-CSS
- Treating Physician*s, Caregiver*s (if applicable), and Patient*s (if able)

Clinical Global Impression of Severity (CGI-S)

Study description

Background summary

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 safety profiles of both N-Acetyl-DL-Leucine and N-Acetyl-L-Leucine have been characterized in both preclinical and clinical studies, including observational/ clinical trials in patients with NPC.

The Sponsor's (IntraBio Ltd.) development of Acetyl-Leucine for NPC began with the commercially available racemic mixture, N-acetyl-DL-leucine (*racemate*) In 2015, IntraBio's collaborators first reported in a case series on 12 patients with NPC that N-acetyl-DL-leucine (3 g/day for one week followed by 5 g per day for three weeks) significantly improved the symptoms of NPC.

N-acetyl-DL-leucine was very well tolerated, and no side effects except intermittent dizziness were reported [Bremova et al, 2015]. Later case series demonstrated the neuroprotective, 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] and 13 patients with NPC treated for a minimum of one-year [Kaya et al, 2021]. Primary pharmacology studies in cell and animal models of NPC have directly linked N-Acetyl-L-Leucine's novel, multi-modal mechanism of action with its symptomatic and neuroprotective, disease-modifying effect. These studies have also demonstrated that the L-enantiomer is the active ingredient of the racemate responsible for the neuroprotective, disease modifying effects, and indicate superior clinical effects when used independently. IntraBio is therefore focusing on the development of N-Acetyl-L-Leucine without the presence of D-enantiomer.

Based on this comprehensive body of non-clinical and observational clinical evidence, IntraBio conducted a multinational, open-label, rater-blinded Phase II clinical trial with IB1001 for NPC (IB1001-201). The trial met its primary and key secondary endpoints, demonstrating a statistically significant and clinically meaningful improvement in pediatric and adult patients with NPC [Bremova et al, 2021]. The major findings of the IB1001-201 trial were: first, N-Acetyl-L-Leucine improved symptoms, including gait and stance, upper extremity function, and fine motor skills, which worsened during the post-treatment washout. Second, consistent with its pharmacological action, N-Acetyl-L-Leucine improved cerebellar signs and functioning after 6 weeks. Third, improvement of neurological status was observed across all demographics of patients (age, gender, age of onset, disease severity, etc.) establishing the rationale for IB1001 to be used as a treatment for all NPC patients. Fourth, the low frequency (7 related AEs in 4 patients of 32 participants) and the transient, mild nature of these AEs inform a favorable benefit-risk profile.

Based on these findings, IntraBio is conducting this Phase III randomized,

placebo-controlled, crossover trial investigating the efficacy and safety of N-Acetyl-L-Leucine (IB1001) for the treatment of NPC.

Study objective

This study has been transitioned to CTIS with ID 2023-510278-14-00 check the CTIS register for the current data.

Primary Objective:

In all jurisdictions except the United States (US), the primary objective is to evaluate the efficacy of N-Acetyl-L-Leucine (IB1001) based on the Scale for the Assessment and Rating of Ataxia (SARA) for the chronic treatment of NPC.

In the US, the primary objective is to evaluate the efficacy of N-Acetyl-L-Leucine (IB1001) based on the modified Scale for the Assessment and Rating of Ataxia (mSARA) for the chronic treatment of NPC.

Note: the mSARA is not administered separately to the original SARA scale but rather comprises a subset of domains of the original SARA scale. Therefore, the original SARA will be administered at each visit in all countries

Secondary Objectives:

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

Exploratory Objective:

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

Study design

This is a multinational, randomized, placebo-controlled, double-blinded, cross-over Phase III study.

Patients will be assessed during three study periods: a baseline period, the first intervention period (*Period I*), and the second intervention period (*Period II*).

Patients will be assessed twice during each intervention period. Section 7 of the protocol contains more detailed information on which study assessments and procedures will be conducted for each study period and visit.

Intervention

The study drug is N-Acetyl-L-Leucine (internal development name: IB1001)

formulated as 1000 mg granules for oral suspension in sachet.

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 Granules for oral suspension in Sachet

Description: The granules for oral suspension contain the following excipients:

- Isomalt
- Hypromellose
- Strawberry Flavour

Strawberry flavour contains natural flavouring substances, flavouring preparations, and carrier additives.

- 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 placebo is formulated as granules for oral suspension in a sachet.

The granules for oral suspension contain the following excipients:

- Lactose
- Microcrystalline Cellulose
- Isomalt
- Hypromellose
- Strawberry Flavour
- Citric Acid
- Denatonium Benzoate

Study burden and risks

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]. To ensure the feasibility of this trial, NPC clinical experts [Dr Marc Patterson, MD, Mayo Clinic, Professor Pediatric Neurology] and the heads of multinational NPC patient organizations [Dr William Evans, Chairman Nieman-Pick UK; Joslyn Crowe, Executive Director, National Niemann-Pick Disease Foundation, Inc.] 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 [Dr Marc Patterson, MD, Mayo Clinic, Professor Pediatric Neurology]. The use of these tests was determined together with representatives of the patient community and parents of patients with NPC as being clinically meaningful for the patients and families and reflective of the ability to perform acts of everyday life safely and securely, while at the same time not being exhausting [Dr William Evans, Chairman Nieman-Pick UK, Personal Communication; Joslyn Crowe, Executive Director, National Niemann-Pick Disease Foundation, Inc].

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 78 mL (42 mL for safety analysis, and 24 mL for the PK analysis, 12 mL for research purposes). 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.

Contacts

Public

IntraBio Ltd

Berkeley Street 17-Flat 1
Londen W1J 8EA
GB

Scientific

IntraBio Ltd

Berkeley Street 17-Flat 1
Londen W1J 8EA
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)

Adolescents (16-17 years)

Adults (18-64 years)

Children (2-11 years)

Elderly (65 years and older)

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 ≥ 4 years with a confirmed diagnosis of NPC at the time of signing informed consent. Confirmed diagnosis includes one of the following [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 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 who have undergone one of the following sterilization procedures at least 6 months prior to the first dose: a) hysteroscopic sterilization; b) 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 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 $7 \leq X \leq 34$ 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 (authorized medicines for NPC [e.g. miglustat], 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

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

1. Patients who have any known hypersensitivity or history of hypersensitivity to:
 - a. Acetyl-Leucine (DL-, L-, D-) or derivatives.
 - b. Excipients the IB1001 sachet (namely isomalt, Hypromellose, and Strawberry Flavour).
 - c. Excipients the placebo sachet (namely isomalt, Hypromellose, Strawberry Flavour, Citric acid, microcrystalline cellulose, lactose, denatonium benzoate).
2. Simultaneous participation in another clinical study or participation in any clinical study involving administration of an investigational medicinal product (IMP; *study drug*) for at least 42 days prior to Visit 1. At the discretion of the investigator, Medical Monitor, and Sponsor, the washout period for specific IMPs may be longer based on the pharmacological activity and pharmacokinetics of the drug.
3. Patients with a physical or psychiatric condition which, at the investigator's discretion and in consultation with the Medical Monitor and Sponsor (as applicable), may put the patient at risk, may confound the study results, or may interfere with the patient's participation in the clinical study, i.e. reliably perform study assessments.
4. Known or persistent use, misuse, or dependency of medication, drugs, or alcohol.
5. Current or planned pregnancy or women who are breastfeeding.
6. 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.
7. 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.

8. 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) N-Acetyl-DL-Leucine (e.g. Tanganil®);

b) N-Acetyl-L-Leucine (prohibited if not provided as IMP in the IB1001-301 trial);

c) Sulfasalazine;

d) Rosuvastatin.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	07-07-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N-Acetyl-L-Leucine
Generic name:	N-Acetyl-L-Leucine

Ethics review

Approved WMO

Date: 18-01-2022

Application type: First submission

Review commission: METC Amsterdam UMC

Approved WMO

Date: 08-04-2022

Application type: First submission

Review commission: METC Amsterdam UMC

Approved WMO

Date: 20-04-2022

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 22-04-2022

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 02-11-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

Kamer G4-214

Postbus 22660

1100 DD Amsterdam

020 566 7389

mecamc@amsterdamumc.nl

Approved WMO

Date: 11-12-2023

Application type: Amendment

Review commission: MEC Academisch Medisch Centrum (Amsterdam)

Kamer G4-214

Postbus 22660

1100 DD Amsterdam

020 566 7389

mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-510278-14-00
EudraCT	EUCTR2021-005356-10-NL
ClinicalTrials.gov	NCT05163288
CCMO	NL79787.018.21