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Disease-Modifying, Neuroprotective Effect of N-Acetyl-L-Leucine in Adult and Pediatric Patients With Niemann-Pick Disease Type C

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Abstract

Background and Objectives

N-acetyl-L-leucine (NALL) has been established to improve the neurologic manifestations of Niemann-Pick disease type C (NPC) after 12 weeks in a placebo-controlled trial. In the open-label extension phase (EP) follow-up, data were obtained after 12 and 18 months to evaluate the long-term effects of NALL for NPC.

Methods

This is an ongoing, multinational, multicenter EP. Patients with a genetic diagnosis of NPC aged 4 years or older who completed the placebo-controlled trial were eligible to continue in the EP and receive orally administered NALL 2–3 times per day in 3 tiers of weight-based dosing. The primary end point is the modified 5-domain NPC Clinical Severity Scale (NPC-CSS) (range 0–25 points; lower score representing better neurologic status); data from the EP cohort are compared with the expected annual trajectory of decline (i.e., disease progression) established in natural history studies. Analyses are also performed on exploratory end points, including the 15-domain and 4-domain NPC-CSSs and the Scale for Assessment and Rating of Ataxia (SARA).

Results

Fifty-three patients aged 5–67 years (45.3% female, 54.7% male) were enrolled in the EP. After 12 months, the mean (±SD) change from baseline on the 5-domain NPC-CSS was −0.27 (±2.42) with NALL vs +1.5 (±3.16) in the historical cohort (95% CI −3.05 to −0.48; $p = 0.009$), corresponding to a 118% reduction in annual disease progression. After 18 months, the mean (±SD) change was +0.05 (±2.95) with NALL vs +2.25 (±4.74) in the historical cohort (95% CI −4.06 to −0.35; $p = 0.023$). The 15-domain and 4-domain NPC-CSSs were consistent with the 5-domain NPC-CSS. The improvements in neurologic manifestations demonstrated in the placebo-controlled trial on the primary SARA end point were sustained over the long-term follow-up. NALL was well tolerated, and no treatment-related adverse events or serious reactions occurred.

Discussion

Treatment with NALL was associated with a significant reduction in NPC disease progression after 12 and 18 months, demonstrating a disease-modifying, neuroprotective effect.

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Glossary

ATP = adenosine triphosphate; **EP** = extension phase; **FDA** = Food and Drug Administration; **mITT** = modified intention-to-treat; **NALL** = N-acetyl-L-leucine; **NPC** = Niemann-Pick disease type C; **NPC-CSS** = NPC Clinical Severity Scale; **SARA** = Scale for the Assessment and Rating of Ataxia; **TEAE** = treatment-emergent adverse event.

Trial Registration Information

The trial is registered with ClinicalTrials.gov (NCT05163288; registered December 6, 2021), EudraCT (2021-005356-10). The first patient was enrolled into the EP on March 8, 2023. The trial was funded by IntraBio Inc.

Classification of Evidence

This study provides Class IV evidence that NALL reduces disease progression in NPC.

Introduction

The IB1001-301 clinical trial was a randomized, double-blind, placebo-controlled clinical trial (hereafter referred to as the "parent study") of N-acetyl-L-leucine (NALL) for the treatment of Niemann-Pick disease type C (NPC).[1,2] The trial enrolled pediatric and adult patients with NPC, a rare (incidence 1:100,000), progressive, debilitating, and prematurely fatal autosomal-recessive lysosomal disorder.[3] In the trial, the mean (±SD) change from baseline on the primary Scale for the Assessment and Rating of Ataxia (SARA) endpoint total score was −1.97 ± 2.43 points after 12 weeks of exposure to NALL and −0.60 ± 2.39 points after 12 weeks of placebo (least-squares mean difference −1.28 points; 95% CI −1.91 to −0.65; $p < 0.001$), demonstrating an improvement in neurologic signs and symptoms and functioning on NALL vs placebo. The trial also met all secondary end points. When patients received placebo, after having crossed over from NALL treatment, there was a deterioration in neurologic status, further establishing that treatment with NALL affects neurologic manifestations.[1]

The IB1001-301 clinical trial served as the basis for the marketing approval of NALL (AQNEURSA, levacetylleucine) by the US Food and Drug Administration (FDA) on September 24, 2024. It is also the basis for an ongoing marketing authorization application, currently under review by the European Medicines Agency. Having demonstrated the benefits of treatment with NALL in the parent study, in this extension phase (EP), the aim was to evaluate the long-term safety and efficacy of NALL including potential neuroprotective and disease-modifying effects. In this study, we report the results of this long-term follow-up after 12 and 18 months.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Approval for the study (ClinicalTrials.gov identifier NCT05163288, EudraCT number 2021-005356-10) was obtained from national regulatory authorities in each country (United States—FDA, United Kingdom—Medicines and Healthcare Products Regulatory Authority, Germany—Federal Institute for Drugs and Medical Devices, Slovakia—Štátny ústav pre kontrolu liečiv, Switzerland—Swissmedic, the Netherlands—Central Committee on Research Involving Human Subjects, Czech Republic—State Institute for Drug Control, and Australia—Therapeutic Goods Administration) and the applicable responsible central research ethics committees/institutional review boards for each center (Ethics Committee of Ludwig Maximilian University of Munich [21-1269], National Institute of Child Diseases Bratislava Ethics Committee [EudraCT 2021-005356-10], Ethics Committee of General University Hospital in Prague [56/22 S-MEK], East Midlands—Derby Research Ethics Committee [1004498], Amsterdam UMC Locatie AMC Central Ethics Committee [NL79787.018.21], Mayo Clinic Institutional Review Board [22-001734], Emory University Institutional Review Board [STUDY00003227], Ethics Committee of the Canton of Bern, Switzerland [BASEC 2022-00638], and Victoria Human Research Ethics Committee [HREC/86167/MH-2022]). Written informed consent was obtained for all study participants from the patient or, if applicable, their parent or legal representative. The trial is registered with ClinicalTrials.gov (NCT05163288; registered December 6, 2021), EudraCT (2021-005356-10). The first patient was enrolled into the EP on March 8, 2023.

Participants

The IB1001-301 parent study was a randomized, placebo-controlled, crossover trial comparing orally administered NALL and placebo in patients aged 4 years or older with a diagnosis of NPC. To be eligible for the study, patients must have (1) presented with clinical symptoms and signs referable to NPC, (2) provided informed consent (in minors or adults unable to give informed consent, consent was obtained from a responsible person), and (3) undergone a washout of any prohibited medications (N-acetyl-DL-leucine, NALL, sulfasalazine, or rosuvastatin) for 42 days before screening. The trial was approved by all respective ethics committees/institutional review boards.[2]

Patients who completed the final scheduled visit of the parent study (visit 6) were eligible to continue into an open-label EP under the same trial protocol. The EP was conducted at the same trial sites and with the same investigators, as the parent study. Eligible participants were those (1) who completed parent study visit 6, (2) for whom the investigator determined that continued treatment with NALL may be in their best interest, and (3) who (or their legal representative) provided written informed consent to continue in the EP.

EP Study Design

The EP is an open-label study. The trial consisted of a baseline visit, conducted in tandem with the last visit of the parent study (visit 6). The EP visit was called "visit 7" (4 patients had independent visit 7 consultations conducted at 28, 42, 57, and 64 days after visit 6 to accommodate each family's scheduling requests). After this baseline visit, patients received open-label treatment with NALL for a minimum of 1 year (365 ± 14 days). Visits occurred at 6 months (visit 8, 180 ± 14 days) and after 1 year (visit 9, 365 ± 14 days) (Figure 1). The EP is ongoing. A prespecified analysis was planned after all patients who participated in the parent study and continued into the EP had completed visit 9.

Given the placebo-controlled crossover design of the parent study, 27 patients (51%) were receiving NALL at EP baseline visit 7. Accordingly, it was prespecified that the parent study randomization baseline visit (visit 2) was used as the "baseline" visit for the EP analysis. The approximate duration between baseline (visit 2) and visit 8 was 12 months and between baseline (visit 2) and visit 9 was 18 months. Over these durations, patients received treatment with NALL for approximately 9 months and 15 months, respectively (Figure 1).

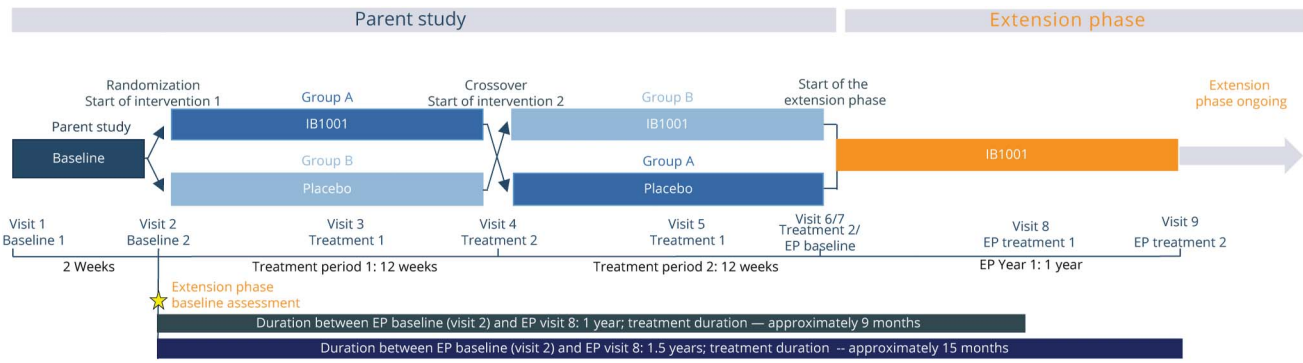
Patients aged 13 years or older or aged 4–12 years weighing ≥35 kg received 4 g/d of orally administered NALL (granules in a sachet for suspension in 40 mL of water, orange juice, or almond milk) 3 times per day (2 g in the morning, 1 g in the afternoon, and 1 g in the evening). Patients aged 4–12 years weighing <35 kg received weight-tiered doses 2 or 3 times per day based on an approximate total dose of 0.1 g/kg/d.

Outcomes

The primary end point of the EP was the modified 5-domain NPC Clinical Severity Scale (NPC-CSS), a 5-item (ambulation, cognition, fine motor skills, speech, and swallow) clinical rating scale ranging from 0 to 25, where 0 is the best neurologic status and 25 the worst.[4] Each domain is rated on a scale of 0–5. The 5-domain NPC-CSS is an abbreviated assessment tool derived from the 17-domain NPC-CSS developed specifically as a clinical outcome assessment to characterize and quantify disease progression in patients with NPC.[5] The 17-domain NPC-CSS consists of 9 major domains (ambulation, cognition, eye movement, fine motor skills, memory, seizures, speech, swallow, hearing) and 8 modifiers (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, and respiratory). In this study, the widely used 15-domain NPC-CSS was applied (which excludes the hearing and auditory brainstem response domains).[3] The 15-domain NPC-CSS has a total score for overall neurologic status ranging from 0 (best) to 54 (worst) and was used as an exploratory end point.

The definitions of response regarding 5-domain and 15-domain NPC-CSS scores were selected to measure deviations from the expected trajectory of disease progression established in the published natural history studies in patients with NPC. Analysis of a cross-sectional evaluation of 37 patients with NPC found that disease progression could be modeled on the 17-domain NPC-CSS using the following equation: $\hat{S}_{t0+x} = \hat{S}_{t0} + 1.87x$, where $\hat{S}_{t0}$ is the initial score and $\hat{S}_{t0+x}$ is the predicted future score after x years.[5] Subsequently, a prospective observational study of 36 patients with NPC reported a mean (±SD) increase of 1.4 ± 2.9 on the 5-domain NPC-CSS (corresponding to an annualized progression rate of 1.5 points) and 2.7 ± 4.0 on the NPC-CSS (excluding hearing) after 12 months.[6]

Figure 1 IB1001-301 EP Scheme



EP = extension phase.

In the abovementioned studies, a linear annualized increase (independent of age at disease onset and similar in all patients) has been documented on the 5-domain NPC-CSS, reflecting the progressive neurodegenerative nature of NPC. Therefore, a higher score indicates a clinical worsening (disease progression) while a lower 5-domain NPC-CSS score indicates a clinical improvement and disease modification. A 0-point change represents a stabilization of disease progression, which is also a significant clinical benefit for rapidly progressive, neurodegenerative diseases such as NPC.

In a recent 12-month, double-blind, randomized placebo-controlled trial with the agent arimoclomol, the mean progression after 12 months in the 16 patients receiving placebo was 2.15 points on the 5-domain NPC-CSS and 2.7 points on the NPC-CSS.[7] However, for the sake of this analysis, the conservative, validated linear natural history cohort values have been used as the basis for comparison, potentially underestimating the clinical deterioration in untreated patients.

Exploratory end points included the SARA, an 8-item (gait, stance, sitting, and speech disturbance, as well as the finger-chase test, the nose-to-finger test, the fast alternating hand movements test, and the heel-along-shin slide test) clinical rating scale that incorporates functional assessments of gait, balance, speech, fine motor function, and upper/lower extremity function; scores range from 0 to 40, with lower scores indicating better neurologic status.[8] The 4-domain NPC-CSS (the 5-domain NPC-CSS with rescored swallow domain and excluding the cognition domain), which served as the basis for the FDA marketing authorization of the combination therapy arimoclomol and miglustat, was also analyzed.[9]

Safety assessments included monitoring for adverse events (whereby the site investigators or their delegates assessed the relation of the event to NALL), clinical laboratory testing and full pharmacokinetic sampling, physical examination, evaluation of vital signs, and electrocardiography.

Statistical Analysis

The number of patients entering the EP was determined by the number of patients completing the parent study (visit 6) and who consented to participate in the open-label follow-up with NALL. The primary end point was defined as the numerical difference of the 5-domain NPC-CSS value for patients treated with NALL at baseline (visit 2) vs 12 months (visit 8) and 18 months (visit 9) evaluated against benchmark annual mean rates of progression from the historical cohorts under the standard of care of 1.5 points annually for the 5-domain NPC-CSS and 1.87 points annually for the 15-domain NPC-CSS.

An independent-sample *t* test at a 2-sided 5% significance level was used to test the null hypotheses that the mean change from the extension baseline on the 5-domain NPC-CSS and the 15-domain NPS-CSS is equal to or greater than the change at 12 months or 18 months expected in the natural history cohorts. The mean and standard deviation for the 18-month historical control cohort were modeled based on the formulas for the annualized increase. Point estimates and 95% CIs of the mean difference are presented. The mean differences are also presented for the primary 5-domain NPC-CSS for key subgroups, including pediatric and adult patients and patients on miglustat or not receiving background miglustat.

The mean change from the extension baseline and 95% CIs are computed for the exploratory end points: 4-domain NPC-CSS and SARA. A 1-sample *t* test at 2-sided 5% significance level was used to test whether the change in SARA from extension baseline differed from zero after 12 and 18 months; since no historical data exists on the 4-domain NPC-CSS, this end point was reported descriptively.

For the 4-domain, 5-domain, 15-domain NPC-CSS scores and the SARA score, descriptive tables are presented with data available from all published or publicly presented previous natural history cohorts and clinical trial cohorts. The data are presented for each scale at 12 months (consistent with what is available in the literature and public domain) (Tables 1–4). The mean and SD (if available) for each cohort are presented, along with the mean difference from the IB1001-301 NALL EP cohort. If available, for clinical trial cohorts treated with drug therapies, the data with and without miglustat on each scale at 12 months are presented.

The primary analysis was performed according to the modified intention-to-treat (mITT) principle, used to estimate the treatment effect regardless of discontinuation and to provide a perspective of the treatment effect across the entire population. The EP mITT analysis set consisted of all patients aged 4 years and older who received at least 1 dose of study drug (NALL) in the EP, and with NPC-CSS scores at extension analysis baseline (visit 2) and during EP treatment period I (visit 8 or visit 9).

The safety analysis EP set consisted of all patients who received at least 1 dose of study drug in the EP. The safety, integrity, and feasibility of the trial were monitored by an independent data safety monitoring board consisting of 3 independent, nonparticipating members (including 2 clinicians and a statistician).

Data Availability

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The study sponsor, IntraBio Inc. is committed to providing qualified scientific researchers appropriate access to anonymized data and clinical study information from the company's clinical trials for the purpose of conducting legitimate scientific research. Requests for specific data will be considered along with the rationale, description of use need, and clinical value of the proposed analysis. IntraBio supports an approach to sharing data that responsibly reflects the interests of all parties involved in clinical trials, including protecting the rights and privacy of

Table 1 Comparison of the 5-Domain NPC-CSS Scores While Receiving NALL With Those of Historical and Clinical Trial Cohorts

Cohort	12 mo from baseline			
	n	Mean change from baseline[a]	% Change from baseline[b]	Mean difference vs IB1001-301 EP cohort (NALL)
IB1001-301 extension phase cohort (NALL)[c]	49	−0.27 (SD = 2.42)	−18%	N/A
Patients on NALL + miglustat	41	−0.17 (SD = 2.53)	−11%	N/A
Patients on NALL (no miglustat)	8	−0.75 (SD = 1.83)	−50%	N/A
Mengel et al., 2020[6] (natural history cohort)	32	+1.5 (SD = 3.16)	+100%	+1.77
Arimoclomol-treated cohort (from arimoclomol phase II/III trial)[7,d]	34	+0.76 (SD = 2.4)	+51%	+1.03
Patients on arimoclomol + miglustat[7]	26	−0.06 (N/A)	−4%	+0.11
Patients on arimoclomol (no miglustat)[7]	8	+4.2 (N/A)	+280%	+4.95
Placebo-treated cohort (from arimoclomol phase II/III trial)[7,e]	16	+2.15 (SD = 2.25)	+143%	+2.42

Abbreviations: EP = extension phase; NALL = N-acetyl-L-leucine; NPC-CSS = Niemann-Pick disease type C Clinical Severity Scale.
[a] A higher score represents disease worsening; a lower score reflects disease improvement.
[b] Calculated based on an annualized progression rate of 1.5 points (representing a +100% rate of annual progression); a positive value reflects disease progression; 0 reflects no change; a negative value reflects disease reversal.
[c] Includes patients treated with NALL (no miglustat) (n = 8) and patients treated with NALL + miglustat (n = 41).
[d] Includes patients treated with arimoclomol (without miglustat) (n = 8) and patients treated with arimoclomol + miglustat combination therapy (n = 26).
[e] Includes patients treated with placebo (no miglustat) (n = 4) and placebo + miglustat (n = 12).

trial participants, the innovator's intellectual property rights, and other incentives for innovation, and as such, will evaluate requests for sharing company clinical trial data with qualified external scientific researchers. Requests to access the data from this clinical trial may be made at info@intrabio.com. Data will be made available for request after product approval in the United States and European Union, after product development is discontinued, or as otherwise required by law or regulation. There are circumstances that may prevent the sponsor from sharing the requested data because the product is investigational at this time.

Results

Study Population

Between March 8, 2023, and August 15, 2023, 53 patients were enrolled in the EP (aged 5–67 years). The demographic

Table 2 Comparison of the NPC-CSS Scores While Receiving NALL With Those of Historical Cohorts and Clinical Trial Cohorts

Cohort	12 mo from baseline			
	n	Mean change from baseline[a]	% Change from baseline[b]	Mean difference vs IB1001-301 EP cohort (NALL)
IB1001-301 extension phase cohort (NALL)[c]	49	0.0 (SD = 3.25)	−3%	N/A
Yanjanin et al., 2010[5] (natural history cohort)	37	+1.87 (SD = 1.1)	+100%	+1.87
Ory et al., 2017[18] (natural history cohort)	21	+2.92 (SD = 1.24)	+156%	+2.92
Mengel et al., 2020[6] (natural history cohort)	32	+2.94 (SD = 4.5)	+157%	+2.94
Arimoclomol-treated cohort[d]	34	+1.20 (SD = 4.75)	+64%	+1.20
Placebo-treated cohort (from arimoclomol phase II/III trial)[7,e]	16	+2.81 (SD = 4.2)	+150%	+2.81

Abbreviations: EP = extension phase; NALL = N-acetyl-L-leucine; NPC-CSS = Niemann-Pick disease type C Clinical Severity Scale.
[a] A higher score represents disease worsening; a lower score reflects disease improvement.
[b] Calculated based on an annualized progression rate of 1.87 points (representing a +100% rate of annual progression); a positive value reflects disease progression; 0 reflects no change; a negative value reflects disease reversal.
[c] Includes patients treated with NALL (no miglustat) (n = 8) and patients treated with NALL + miglustat (n = 41).
[d] Includes patients treated with arimoclomol (without miglustat) (n = 8) and patients treated with arimoclomol + miglustat combination therapy (n = 26).
[e] Includes patients treated with placebo (no miglustat) (n = 4) and placebo + miglustat (n = 12).

Table 3 Comparison of the 4-Domain NPC-CSS Scores While Receiving NALL With Those of Clinical Trial Cohorts

Cohort	12 mo from baseline		
	n	Mean change from baseline[a]	Mean difference vs IB1001-301 EP cohort (NALL)
IB1001-301 extension phase cohort (NALL)[b]	49	−0.59 (SD = 1.79)	N/A
Patients on NALL + miglustat	41	−0.59 (SD = 1.86)	N/A
Patients on NALL (no miglustat)	8	−0.63 (SD = 1.51)	N/A
Arimoclomol-treated cohort (from arimoclomol phase II/III trial)[19,c]	34	+0.62 (SD = 0.39)	+1.21
Patients on arimoclomol + miglustat[9]	22	−0.2 (SD = 1)	+0.39
Patients on arimoclomol (no miglustat)[19]	8	+4.13 (N/A)	+4.27
Placebo-treated cohort (from arimoclomol phase II/III trial)[19,d]	16	+2.12 (SD = 0.59)	+2.71
Patients on placebo + miglustat[9]	12	+2.0 (SD = 0.7)	+2.59
Patients on placebo (no miglustat)[19]	3	+1.98 (N/A)	+2.57

Abbreviations: EP = extension phase; NALL = N-acetyl-L-leucine; NPC-CSS = Niemann-Pick disease type C Clinical Severity Scale.
[a] A higher score represents disease worsening; a lower score reflects disease improvement.
[b] Includes patients treated with NALL (no miglustat) (n = 8) and patients treated with NALL + miglustat (n = 41).
[c] Includes patients treated with arimoclomol (no miglustat) (n = 8) and patients treated with arimoclomol + miglustat combination therapy (n = 26).
[d] Includes patients treated with placebo (no miglustat) (n = 4) and placebo + miglustat (n = 12).

and baseline clinical characteristics of the enrolled patients are presented in Table 5. Forty-nine patients qualified for the primary EP mITT analysis set (92.4%), which included all patients dosed who had an NPC-CSS score at baseline and at least 1 EP treatment visit (visit 8 or visit 9). Three patients did not have an NPC-CSS score at baseline because of accidentally missed assessment and thus were not included; 1 patient was withdrawn after visit 7 following withdrawal of consent.

Visit 8 occurred approximately 1 year after the baseline visit (visit 2) during which patients received treatment with NALL for approximately 9 months (mean duration of 268 [min 233, max 287] days out of mean 354 days [min 317, max 371]). Visit 9 occurred approximately 18 months after the baseline visit (visit 2) during which patients received treatment with NALL for approximately 15 months (mean duration of 453 [min 435, max 556] days out of 539 days [min 520, max 633]) (Figure 1). The EP remains ongoing for additional years of long-term follow-up.

Efficacy

Primary End Point

The mean (±SD) baseline (visit 2) score on the 5-domain NPC-CSS was 11.10 (±4.73). After 12 months (visit 8), the mean change from baseline was −0.27 ± 2.42 points with NALL vs 1.5 ± 3.1 points in the historical cohort (mean difference −1.77 points; 95% CI −3.05 to −0.48; $p = 0.009$). After 18 months (visit 9), the mean change from baseline was +0.045 ± 2.95 with NALL vs 2.25 (4.74) in the historical cohort (mean difference −2.20 points; 95% CI −4.06 to −0.35; $p = 0.023$). Table 1 and Figure 2 present the change on the 5-

Table 4 Comparison of the SARA Scores While Receiving NALL With Those of Clinical Trial Cohorts

Cohort	12 mo from baseline		
	n	Mean change from baseline[a]	Mean difference vs IB1001-301 EP cohort (NALL)
IB1001-301 extension phase cohort (NALL)[b]	51	−1.88 (SD = 2.89)	N/A
Arimoclomol-treated cohort (from arimoclomol phase II/III trial)[7,c]	34	+1.06 (SD = 3.66)	+2.94 (SE = 0.75)
Placebo-treated cohort (from arimoclomol phase II/III trial)[7,d]	16	+0.78 (SD = 1.62)	+2.66 (SE = 0.57)

Abbreviations: EP = extension phase; NALL = N-acetyl-L-leucine; SARA = Scale for Assessment and Rating of Ataxia.
[a] A higher score represents a worsening of neurologic status; a lower score represents an improvement in neurologic status.
[b] Includes patients treated with NALL (no miglustat) (n = 8) and patients treated with NALL + miglustat (n = 43).
[c] Includes patients treated with arimoclomol (no miglustat) (n = 8) and patients treated with arimoclomol + miglustat combination therapy (n = 26).
[d] Includes patients treated with placebo (no miglustat) (n = 4) and placebo + miglustat (n = 12).

Table 5 IB1001-301 EP Demographics and Baseline Characteristics

Parameter	Total (n = 53)
Age, n (%)	
Pediatric (<18 y)	22 (41.5)
Adult (≥18 y)	31 (58.5)
Sex, n (%)	
Female	24 (45.3)
Male	29 (54.7)
Race, n (%)	
American Indian or Alaska Native	0 (0.0)
Asian	2 (3.8)
Black or African American	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)
White	47 (88.7)
Other	4 (7.5)
Age at diagnosis group, n (%)	
Early-infantile (<2 y)	9 (17.0)
Late-infantile (2–<6 y)	13 (24.5)
Juvenile (6–<15 y)	21 (39.6)
Adolescent/adult (≥15 y)	10 (18.9)
Dose group, n (%)	
Age 4–12 y: 15–<25 kg: 2 g/d	5 (9.4)
Age 4–12 y: 25–<35 kg: 3 g/d	3 (5.7)
Age 4–12 y: ≥35 kg or age ≥13 y: 4 g/d	45 (84.9)
Miglustat at baseline, n (%)[a]	
Yes	45 (84.9)
No	8 (15.1)

Abbreviation: EP = extension phase.
[a] Indicates concurrent miglustat use throughout the duration of the trial.

domain NPC-CSS with NALL compared with all published historical cohorts and clinical trial cohorts.

Subgroup analysis of pediatric vs adult patients demonstrated consistent benefit with NALL. After 12 months (visit 8), the mean change from baseline was −0.10 ± 3.16 points for pediatric patients and −0.39 ± 1.73 for adult patients. After 18 months (visit 9), the mean change from baseline was −0.21 ± 3.49 for pediatric patients and +0.24 ± 2.52 for adult patients.

Exploratory End Points

The mean (±SD) baseline (visit 2) score on the 15-domain NPC-CSS was 18.28 (±6.98). After 12 months (visit 8), the mean change from baseline was 0.0 ± 3.25 points with NALL vs 1.87 ± 1.09 points in the historical cohort (mean difference −1.87; 95% CI −2.83 to −0.87; $p < 0.001$). After 18 months (visit 9), the mean change from baseline was 0.43 ± 4.65 with NALL vs 2.81 ± 1.64 in the historical cohort (mean difference −2.37; 95% CI −3.85 to −0.90; $p = 0.002$). Table 2 presents the change on the 15-domain NPC-CSS with NALL compared with all published historical cohorts and clinical trial cohorts.

The mean (±SD) baseline (visit 2) score on the 4-domain NPC-CSS was 8.14 (±3.58). After 12 months (visit 8), the mean change from baseline was −0.59 ± 1.79 points with NALL. After 18 months (visit 9), the mean change from baseline was −0.27 ± 2.29 with NALL. Table 3 presents the change on the 4-domain NPC-CSS with NALL compared with all publicly available cohorts.

The mean (±SD) baseline (visit 2) score on the SARA was 15.91 (7.65). After 12 months (visit 8), the mean change from baseline was −1.88 ± 2.89 points with NALL (95% CI −2.70 to −1.07; mean change = 0, $p < 0.001$). After 18 months (visit 9), the mean change from baseline was −1.64 ± 3.24 with NALL (95% CI −2.59 to −0.69, mean change = 0, $p < 0.001$). There was no significant difference between these values and those from the completion of the parent study; rather, the improvements on the SARA were sustained across long-term treatment. Table 4 presents the change on the SARA with NALL compared with all published cohorts.

Safety

No treatment-emergent adverse events (TEAEs) led to premature discontinuation of the trial. No TEAEs occurred in more than 10% of patients on NALL, and no patients had TEAEs that were assessed by the investigator as related to NALL.

No trial drug–related serious adverse events or deaths occurred. Results of plasma and urine tests, vital signs, and ECG recordings were normal or rated as clinically nonsignificant. Adherence to the trial drug was high as shown by treatment compliance and the regular urine analyses for prohibited medication.

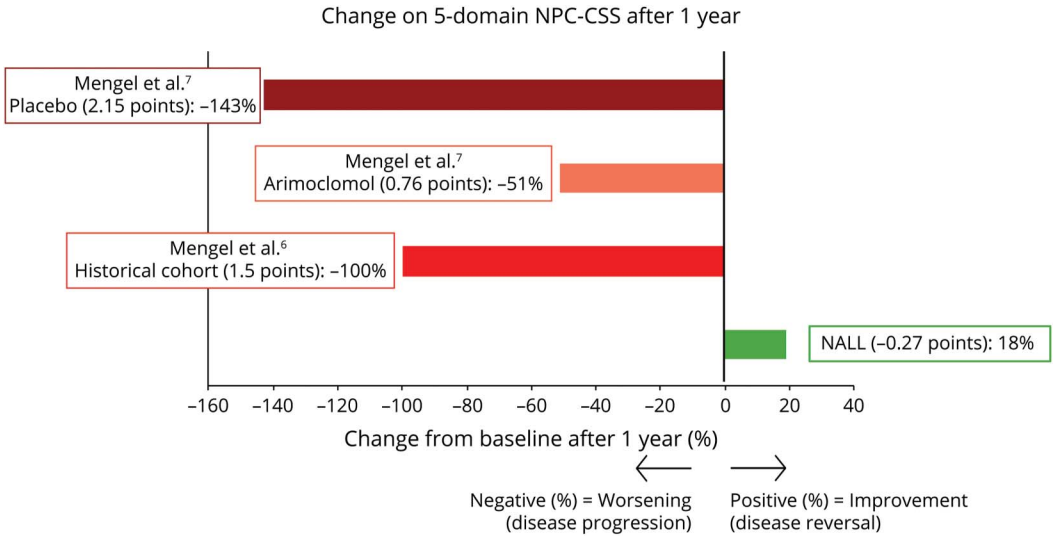
Classification of Evidence

This study provides Class IV evidence that NALL reduces disease progression in NPC.

Discussion

In this study, we present findings from the largest cohort of patients with NPC treated in the frame of a long-term clinical trial. The major findings of this study are as follows: in adult and pediatric patients with NPC, treatment with NALL was associated with a 118% reduction in annual disease progression after 1 year compared with a natural history control cohort, on the 5-domain NPC-CSS primary end point,

Figure 2 Bar Plot for the 5-Domain NPC-CSS Total Score vs Those of Published Historical Cohorts and Clinical Trial Cohorts



Percentage calculated based on the annualized progression rate of 1.5 points (representing a −100% rate of annual progression); a negative value reflects disease worsening/progression; 0 reflects no change (disease stabilization); and a positive value reflects disease improvement. NPC-CSS = Niemann-Pick disease type C Clinical Severity Scale.

reflecting a significant improvement in the patient's condition from 1 year before. After 1 year, there was a reduction of −0.27 points from baseline (compared with a 1.5-point increase in the historical cohort) on a 25-point scale used to assess neurologic status in multiple domains and disease progression in NPC, and a change of 0.0 after 1.5 years (vs the expected +2.25-point change). This improvement is to date the most significant of any agent formally investigated in NPC (Tables 1–3; Figure 2).

In the randomized, double-blind parent study, NALL demonstrated a significant improvement in neurologic signs and symptoms after 12 weeks. The improvement in neurologic manifestations and status demonstrated with NALL vs placebo on the SARA was maintained after 12 and 18 months of treatment, demonstrating a statistically significant and clinically meaningful improvement[10] and the long-term effects of NALL. No new safety signals and no drug-related serious adverse events were observed during the follow-up, reinforcing the benign safety profile of the molecule.

The improvement on the 5-domain NPC-CSS with NALL is clinically meaningful according to the validation of the 5-domain NPC-CSS, which demonstrated that a 1-point worsening on the 5-domain NPC-CSS constitutes a clinically meaningful change for caregivers/parents and physicians (e.g., a 1-point change or greater represents a clinically meaningful transition reflecting loss of complex function and increased disability), and therefore, preventing a 2-point worsening would be a viable treatment goal.[11] Treatment with NALL not only prevented worsening (e.g., halted disease progression) on the 5-domain NPC-CSS but led to an improvement, demonstrating a neuroprotective and disease-modifying benefit. This benefit was demonstrated both in patients who were and were not receiving miglustat, reflecting NALL's efficacy as a standalone and consistent with results from the placebo-controlled parent study (where NALL improved neurologic signs, symptoms, and quality of life irrespective of background miglustat use) (Table 1).[1]

The findings from this extension trial are consistent with NALL's mechanism of action (MOA). The acetylation of leucine makes it a substrate for ubiquitously expressed monocarboxylate transporters, delivering *supraphysiological* levels of NALL relative to leucine into the cell's cytoplasm.[12] There, NALL is deacetylated, yielding L-leucine, which enters enzyme-controlled pathways to correct metabolic dysfunction. For example, in the NPC mouse model ($Npc1^{-/-}$), NALL leads to changes in Krebs cycle flux, shifting glucose metabolism from lactate/lactate dehydrogenase toward pyruvate/pyruvate dehydrogenase dependency, resulting in a significant improvement in adenosine triphosphate (ATP) production.[13] Knock-on effects of restoring more efficient ATP synthesis include mitigating dysfunctional lysosome fusion and trafficking, resulting in reduced accumulation of cholesterol, sphingosines, and glycosphingolipids.[13] The consequences of restoring mitochondrial and lysosomal function include normalization of neuronal membrane potential, restoring cellular signaling,[14] and dampening of neuroinflammation, leading to an overall reduction in neurodegeneration.[13,15,16]

The disease-modifying effects of NALL have been clearly demonstrated in the NPC ($Npc1^{-/-}$) mice. Presymptomatic treatment of $Npc1^{-/-}$ mice with NALL from 3 weeks of age delayed the onset of functional decline (gait abnormalities, motor dysfunction), delayed the decline in general health

(including coat grooming and weight), slowed disease progression, and prolonged survival. These neuroprotective effects were observed solely in animals exposed to the L-enantiomer (absent in animals treated with N-acetyl-D-leucine).[13]

Finally, these findings are consistent with other studies of this agent for common neurologic conditions. For example, NALL restored autophagic flux and its neuroprotective function in the cortices of mice with traumatic brain injury, leading to the attenuation of neuroinflammation and restriction of neuronal cell death, reflecting a neuroprotective effect.[15,16] More recently, published observational studies in patients with prodromal Parkinson disease (REM sleep behavior disorder) used molecular imaging techniques in the brains of patients to show that acetyl-leucine stopped the decline of neuronal function at the cellular and molecular level and reversed changes in the biomarker for prodromal alpha-synucleinopathies, preventing the clinical conversion to manifest Parkinson disease.[17]

Limitations of the trial include the open-label design. Analyses were not adjusted for multiple comparisons. The data of the historical cohort were not made publicly available; thus, it was not possible to match the historical cohort with the IB1001-301 EP patient population. Nevertheless, the IB1001-301 EP study population was significantly larger (31 vs 54 patients with continued follow-up). However, owing to the inclusion criteria of the parent study, the EP did not include patients aged younger than 4 years, asymptomatic patients, or patients with advanced disease who would not be able, or reliably able, to complete functional assessments. Although the comparison with historical cohorts was valuable, the lack of a placebo control group in the extension phase introduced a potential for bias. Finally, in the context of this progressive neurodegenerative disorder, longer periods of observation will be beneficial to determine the full safety and efficacy data of NALL.

In conclusion, this study provides additional evidence of the benefits of NALL treatment. NALL represents a new class of therapeutic agent that acts as a metabolic modulator, rebalancing dysregulated energy metabolism, and is pleiotropic in its effects. NALL is the first and only compound that has demonstrated both rapid improvements in neurologic manifestations and a long-term, disease-modifying, neuroprotective effect for patients with NPC. In light of its efficacy and safety profile, NALL should be considered a foundational and cornerstone therapy for the treatment of NPC. In addition, given the broad applicability of its mechanism, NALL should continue to be investigated for the treatment of a plethora of rare and common neurologic disorders.

Author Contributions

M.C. Patterson: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. U. Ramaswami: major role in the acquisition of data. A. Donald: major role in the acquisition of data. T. Foltan: major role in the acquisition of data. M. Gautschi: major role in the acquisition of data. P. Gissen: major role in the acquisition of data. A. Hahn: major role in the acquisition of data. S.A. Jones: major role in the acquisition of data. R. Kay: study concept or design; analysis or interpretation of data. M. Kolniková: major role in the acquisition of data. J. Park: major role in the acquisition of data. S. Reichmannová: major role in the acquisition of data. M. Walterfang: major role in the acquisition of data. P. Wibawa: major role in the acquisition of data. M. Rohrbach: analysis or interpretation of data. K. Martakis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Bremova-Ertl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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