ORIGINAL ARTICLE

Trial of *N*-Acetyl-L-Leucine in Niemann–Pick Disease Type C

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ABSTRACT

BACKGROUND

Niemann–Pick disease type C is a rare lysosomal storage disorder. We evaluated the safety and efficacy of *N*-acetyl-L-leucine (NALL), an agent that potentially ameliorates lysosomal and metabolic dysfunction, for the treatment of Niemann–Pick disease type C.

METHODS

In this double-blind, placebo-controlled, crossover trial, we randomly assigned patients 4 years of age or older with genetically confirmed Niemann–Pick disease type C in a 1:1 ratio to receive NALL for 12 weeks, followed by placebo for 12 weeks, or to receive placebo for 12 weeks, followed by NALL for 12 weeks. NALL or matching placebo was administered orally two to three times per day, with patients 4 to 12 years of age receiving weight-based doses (2 to 4 g per day) and those 13 years of age or older receiving a dose of 4 g per day. The primary end point was the total score on the Scale for the Assessment and Rating of Ataxia (SARA; range, 0 to 40, with lower scores indicating better neurologic status). Secondary end points included scores on the Clinical Global Impression of Improvement, the Spinocerebellar Ataxia Functional Index, and the Modified Disability Rating Scale. Crossover data from the two 12-week periods in each group were included in the comparisons of NALL with placebo.

RESULTS

A total of 60 patients 5 to 67 years of age were enrolled. The mean baseline SARA total scores used in the primary analysis were 15.88 before receipt of the first dose of NALL (60 patients) and 15.68 before receipt of the first dose of placebo (59 patients; 1 patient never received placebo). The mean (±SD) change from baseline in the SARA total score was –1.97±2.43 points after 12 weeks of receiving NALL and –0.60±2.39 points after 12 weeks of receiving placebo (least-squares mean difference, –1.28 points; 95% confidence interval, –1.91 to –0.65; P<0.001). The results for the secondary end points were generally supportive of the findings in the primary analysis, but these were not adjusted for multiple comparisons. The incidence of adverse events was similar with NALL and placebo, and no treatment-related serious adverse events occurred.

CONCLUSIONS

Among patients with Niemann–Pick disease type C, treatment with NALL for 12 weeks led to better neurologic status than placebo. A longer period is needed to determine the long-term effects of this agent in patients with Niemann–Pick disease type C. (Funded by IntraBio; ClinicalTrials.gov number, NCT05163288; EudraCT number, 2021-005356-10.)

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Niemann–Pick disease type C is a rare, progressive, debilitating, and prematurely fatal autosomal recessive lysosomal storage disorder, with an incidence of one case per 100,000 persons.[1] The disease manifests with systemic, psychiatric, and neurologic symptoms, and many aspects of neurologic function are impaired.[2] Treatment of Niemann–Pick disease type C is currently limited to slowing the progression of neurologic symptoms with miglustat, a drug used in substrate reduction therapy for glycosphingolipid lysosomal storage disorders. Miglustat has been approved in the European Union and several other countries but not in the United States.[3]

N-acetyl-L-leucine (NALL) is the L-enantiomer of *N*-acetyl-DL-leucine. The agent is administered orally and is taken up by monocarboxylate transporters, which are expressed ubiquitously and thus deliver NALL to all body tissues, including across the blood–brain barrier.[4] The agent enters enzyme-controlled pathways that correct metabolic dysfunction and improves adenosine triphosphate (ATP) energy production. Such correction and improvement have multiple subsequent effects: mitochondrial and lysosomal functions are intrinsically linked, and the normalization of energy metabolism ameliorates lysosomal dysfunction and leads to a reduction in the storage of unesterified cholesterol and sphingolipids.[5] At a cellular level, the depletion of ATP causes neuronal depolarization, leading to the failure of membrane-based ion-transport systems and defective membrane excitability that affects neuronal communication. Treatment with NALL was shown to normalize neuronal membrane potentials in a guinea pig model, thereby ostensibly improving cellular signaling processes and restoring and protecting neuronal circuits.[6] In various animal models, treatment with NALL has led to dampening of neuroinflammation, which indicates a potential neuroprotective effect.[5,7]

In an *Npc1*$^{-/-}$ mouse model of Niemann–Pick disease type C, treatment with NALL delayed the onset of functional decline (gait abnormalities and motor dysfunction) and the decline in general health, coat condition, and body weight; slowed disease progression; and prolonged survival. These effects were observed solely in the L-enantiomer and were lacking in animals treated with *N*-acetyl-D-leucine.[5] In mouse models, treatment with NALL reduced motor dysfunction, ataxia, and gait dysfunction before or after the onset of symptoms. The dose used in these animal studies (0.1 g per kilogram of body weight per day) is equivalent to the dose used in clinical studies[8,9] and in the current clinical trial.

A multinational, assessor-blinded, phase 2b clinical trial involving children and adults with Niemann–Pick disease type C showed that treatment with NALL resulted in reductions in symptoms and improvements in functioning and quality of life after 6 weeks of treatment.[10] In the current phase 3, randomized, placebo-controlled trial, we evaluated the efficacy and safety of NALL in pediatric and adult patients with Niemann–Pick disease type C over 12 weeks of treatment.

METHODS

TRIAL OVERSIGHT

The trial was sponsored by IntraBio, which designed the trial, supplied the active drug and matching placebo, and contracted out the data analyses. The trial was conducted at 13 trial sites across Australia, the Czech Republic, Germany, the Netherlands, Slovakia, Switzerland, the United Kingdom, and the United States. Confidentiality agreements were in place between IntraBio and each trial site or investigator, according to local legislation.

The trial was approved by a central research ethics committee or an institutional review board at each center. The safety, integrity, and feasibility of the trial were monitored by an independent data and safety monitoring board consisting of two clinicians and a statistician. Cetara, a drug development consultancy, performed the statistical analyses. The authors had access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The authors made the decision to submit the manuscript for publication with no need for approval by the sponsor.

PATIENTS

Patients 4 years of age or older who had received a diagnosis of Niemann–Pick disease type C were eligible for inclusion if they had presented with clinical symptoms and signs referable to Niemann–Pick disease type C, had provided written informed consent (or consent had been provided by a legal representative), and had under-

taken a washout of any prohibited medications (i.e., *N*-acetyl-DL-leucine, *N*-acetyl-L-leucine, sulfasalazine, or rosuvastatin) for 42 days before screening. The total score on the Scale for the Assessment and Rating of Ataxia (SARA) had to be between 7 and 34, which represents a range of mild to severe symptoms (scores range from 0 to 40, with lower scores indicating better neurologic status). Additional details regarding the SARA total score are provided in the End Points section below. The eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Details of the trial rationale, design, methods, and objectives were published previously[11] and are provided in the protocol. The trial consisted of a 2-week baseline period followed by two consecutive 12-week treatment periods; the baseline and treatment periods included a 7-day window for the last visit after the intended 2 or 12 weeks, respectively (Fig. 1). Two visits (occurring 14 to 21 days apart) were conducted in the baseline period. Safety and efficacy assessments were performed at both visits. At the second baseline visit (visit 2), eligible patients were randomly assigned in a 1:1 ratio to receive NALL in period 1 for 84 to 91 days and then matching placebo in period 2 for 84 to 91 days (sequence 1) or to receive placebo in period 1 for 84 to 91 days and then NALL in period 2 for 84 to 91 days (sequence 2). NALL or placebo was immediately switched at the end of period 1 (visit 4).

Randomization was performed by Medpace, a clinical research organization, with the use of computerized interactive response technology. Two visits occurred in each period, with visits 3 and 4 occurring in period 1 and visits 5 and 6 occurring in period 2. The patients, the families and caregivers of the patients, the investigators and trial teams, and the representatives of the sponsor were unaware of the trial-group assignments until the database was locked for analysis. Patients who had completed the trial at visit 6 were eligible to continue treatment with NALL in an open-label, long-term extension phase, which was prespecified in the original protocol and is currently ongoing.

During the two treatment periods, patients 13 years of age or older and those 4 to 12 years of age and weighing at least 35 kg received NALL or matching placebo orally at a dose of 4 g per day. The placebo was developed to have the same color, taste, appearance, and solubility properties as the active agent, and both were packaged as granules in a sachet for suspension in 40 ml of water, orange juice, or almond milk three times per day (2 g in the morning, 1 g in the afternoon, and 1 g in the evening). Patients 4 to 12 years of age and weighing less than 35 kg received NALL or placebo two or three times per

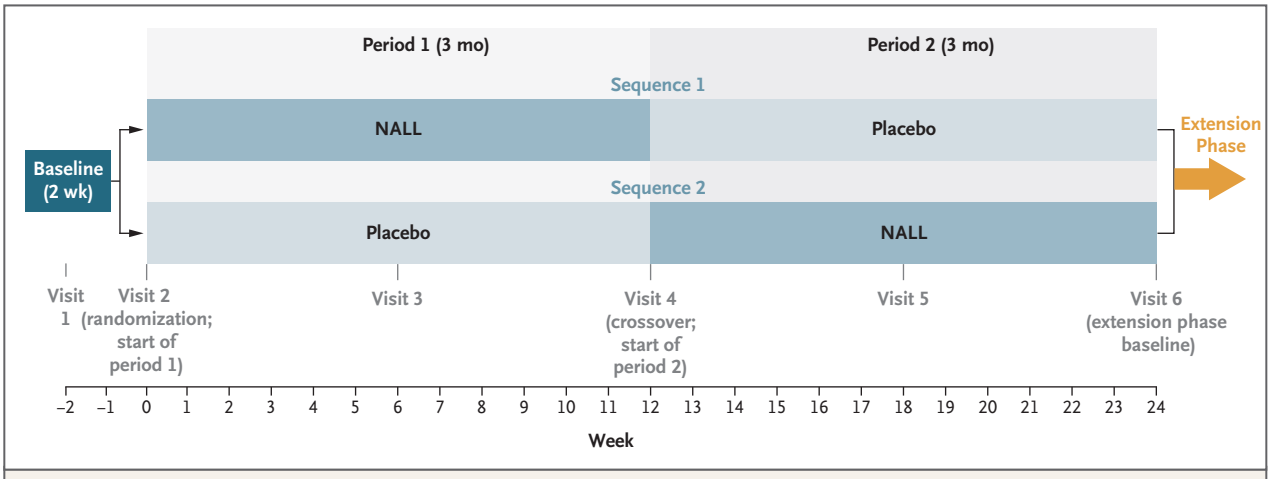

Figure 1. Trial Design.

The patients were randomly assigned in a 1:1 ratio to receive *N*-acetyl-L-leucine (NALL) for 12 weeks in period 1, followed by placebo for 12 weeks in period 2 (sequence 1), or to receive placebo for 12 weeks in period 1, followed by NALL for 12 weeks in period 2 (sequence 2). NALL or placebo was immediately switched at the end of period 1 (visit 4).

day in weight-based doses (2 to 4 g per day) that were based on an approximate total dose of 0.1 g per kilogram of body weight per day.

END POINTS

As specified in the original protocol, the primary end point in all jurisdictions, except the United States, was the total score on the SARA, an eight-item clinical rating scale that incorporates assessments of 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.[12] The SARA is a validated clinical scale that measures the severity of neurologic signs and symptoms with internal consistency in patients with spinocerebellar ataxias but has not been validated in patients with Niemann–Pick disease type C. The domains of the SARA are functional, and the total score does not represent an isolated measure of cerebellar ataxia but reflects the various neurologic systems that are impaired in Niemann–Pick disease type C and lead to functional decline.[13]

At the request of the Food and Drug Administration, the total score on a modified SARA (mSARA), in which the sitting and stance domains were excluded, was used as the primary end point in the United States; scores range for 0 to 30, with lower scores indicating better neurologic status. In this article, the SARA total score was used in the primary end-point analysis; the analysis of mSARA total score was considered to be ancillary, and the results are reported without a P value for the between-group differences (NALL vs. placebo).

Secondary end points were the scores on the modified Disability Rating Scale (mDRS), the Spinocerebellar Ataxia Functional Index (SCAFI), the Clinical Global Impression of Improvement (CGI-I) scale, the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) and child-friendly visual-analogue scale (EQ-5D-Y), and exit interviews. The mDRS consists of six subdomains (ambulation, manipulation, seizures, language, swallowing, and ocular movements), with the total score for overall neurologic status ranging from 0 (best) from 24 (worst); scores were then scaled to a range of 0 to 1.[14] The SCAFI, which was used to assess cerebellar function, comprises the timed 8-meter walk test, the timed 9-hole peg test with the dominant and nondominant hand, and the number of spoken repetitions of the bisyllabic phrase "PATA" within 10 seconds. Each test was carried out twice, and the values were averaged; the values for the 8-meter walk test and the timed 9-hole peg test were converted from times (the number of seconds to complete the assessment) to rates (completion of the assessment per second). The SCAFI scores were expressed as a composite z score of each test relative to the baseline scores.[15] Subjective ratings of changes in impairment and quality of life were evaluated by the investigators, the caregivers, and the patients with the use of the CGI-I, a 7-point Likert scale on which scores range from −3 to 3, with −3 indicating very much improved, 0 no change, and 3 very much worse.[16,17]

The score on the Niemann–Pick disease type C Clinical Severity Scale was used as an exploratory measure; scores range from 0 to 54, with 0 indicating the best neurologic status and 54 the worst.[18] This scale was developed and validated for clinical assessment of disease progression, at least 1 year after the last assessment, in patients with Niemann–Pick disease type C. Safety assessments included monitoring for adverse events (whereby the site investigators or their delegates assessed the relation of the event to NALL or placebo), clinical laboratory testing and limited pharmacokinetic sampling, physical examination, evaluation of vital signs, and electrocardiography.

STATISTICAL ANALYSIS

A sample of 46 patients was estimated to provide the trial with 80% power, at a one-sided significance level of 5%, to detect a mean between-group difference (NALL vs. placebo) of 1.0 point in the total score on the SARA and of 0.85 points in the total score on the mSARA, with the assumption, which was based on an analysis of covariance with the baseline total score on the SARA or mSARA at the start of period 1 as the covariate, of a standard deviation between 7.5 and 8.5 points for the SARA total score and between 6.375 and 7.225 points for the mSARA total score. The primary efficacy analyses of the SARA and mSARA total scores were conducted with the use of an analysis of covariance model, with the difference in the SARA or mSARA total score between visit 4 (end of period 1) and visit 6 (end of period 2) as the dependent variable and with the baseline SARA or mSARA total score and an indicator for the sequence

(sequence 1 or 2) as independent variables. The estimated coefficient of the indicator for sequence in this model provides the least-squares mean estimate of the between-group difference when divided by 2. Crossover data from the two 12-week periods in each group were included in the comparisons of NALL with placebo.

This method of analysis accounts for any crossover effects between treatment periods and evaluates the within-patient differences. Statistical analyses were performed in the modified intention-to-treat analysis set, which included all the patients who had undergone randomization and received at least one dose of NALL or placebo at visit 2 (start of period 1). All the patients received at least one dose, and therefore this analysis set corresponded to the intention-to-treat population. One patient withdrew from the trial during period 1, and to accommodate the missing data, we used a mixed-effects model, in which missing data were assumed to be missing at random, as described by Mehrotra.[19] As noted, the SARA total score was used in the primary analysis to avoid issues related to multiple comparisons if the mSARA had been used as an additional primary outcome. Two-sided P values of the null hypothesis were calculated, and a P value of 0.05 or less was considered to indicate statistical significance.

The method used to analyze the primary end point was also used in the analyses of the SCAFI and mDRS scores (secondary end points). In the analysis of the CGI-I scores, the change in score from baseline to the end of period 1 was set as a score of 0 (no change) for all the patients and was assessed in the two randomization groups. For the primary and each secondary end point, separate evaluations were conducted within key subgroups that were defined in the statistical analysis plan, available with the protocol (the trial was not powered for conclusions made on the basis of these subgroups). Because there was no prespecified plan for adjustment for multiple comparisons, the results for secondary end points are presented as point estimates and 95% confidence intervals without P values, and no definite conclusions can be drawn from these data. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute). Safety analyses were performed in the safety analysis set, which included all the patients who had received at least one dose of NALL or placebo.

RESULTS

PATIENTS

A total of 64 patients underwent screening between June 30, 2022, and December 22, 2022, and 60 patients 5 to 67 years of age were enrolled in the trial and underwent randomization. Four patients were excluded because their SARA total scores were outside the range of 7 to 34. The demographic and clinical characteristics of the enrolled patients at baseline are shown in Table 1; the genotype and additional information on the phenotype and clinical characteristics of each patient are shown in Table S3. Table S2 shows the representativeness of the trial population.

A total of 30 patients (50%) were assigned to follow sequence 1 (NALL to placebo) and 30 patients (50%) were assigned to follow sequence 2 (placebo to NALL). One patient who was assigned to follow sequence 1 was withdrawn in period 1 between visit 3 and visit 4 owing to a serious adverse event that was unrelated to trial treatment (complications during a preplanned placement of a percutaneous endoscopic gastrostomy feeding tube that led to a prolonged hospitalization because of aspiration pneumonia, which was fatal). The available data obtained while this patient was receiving NALL in period 1 were used in the primary analysis set by means of the last-observation-carried-forward approach.

The mean (±SD) baseline SARA total scores (set at visit 2) that were used in the primary analysis were 15.88±7.50 before receipt of the first dose of NALL (60 patients) and 15.68±7.39 before receipt of the first dose of placebo (59 patients) (Table 1). In period 1 only, the mean baseline SARA total scores were 14.90±7.49 before receipt of the first dose of NALL (30 patients) and 16.87±7.51 before the first dose of placebo (30 patients). Mean baseline scores for other assessment tools are provided in Table 1. A total of 85% of the patients had been treated with miglustat and continued the treatment throughout the trial. A total of 59 patients (98%) completed the trial.

PRIMARY END POINT

The mean change from baseline in the total score on the SARA was −1.97±2.43 points after 12 weeks of receiving NALL and −0.60±2.39 points after 12 weeks of receiving placebo (least-squares mean

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients (N = 60)
Age group — no. (%)	
Pediatric, <18 yr	23 (38)
Adult, ≥18 yr	37 (62)
Sex — no. (%)	
Female	27 (45)
Male	33 (55)
Race or ethnic group — no. (%)†	
American Indian or Alaska native	0
Asian	0
Black or African American	2 (3)
Native Hawaiian or other Pacific Islander	0
White	54 (90)
Other	4 (7)
Age at diagnosis — no. (%)	
<2 yr	9 (15)
2 to <6 yr	14 (23)
6 to <15 yr	23 (38)
≥15 yr	14 (23)
Duration of disease — mo‡	
Mean	171.32±116.70
Median	153.43
Minimum–maximum range	19.1 to 514.3
Dose group — no. (%)	
Age 4 to 12 yr	
15 to <25 kg of body weight: 2 g per day	6 (10)
25 to <35 kg of body weight: 3 g per day	3 (5)
25 to ≥35 kg of body weight: 4 g per day	3 (5)
Age ≥13 yr: 4 g per day	48 (80)
Miglustat use — no. (%)§	51 (85)
Assessment tool score¶	
SARA‖	
Before first dose of NALL	15.88±7.50
Before first dose of placebo	15.68±7.39
mSARA‖	
Before first dose of NALL	13.20±5.50
Before first dose of placebo	13.03±5.39
SCAFI**	
Before first dose of NALL	−0.29±1.03
Before first dose of placebo	−0.26±1.01
mDRS††	
Before first dose of NALL	0.480±0.149
Before first dose of placebo	0.477±0.149

Table 1. (Continued.)

Characteristic	Patients (N = 60)
NPC-CSS‡‡	
Before first dose of NALL	18.1±7.1
Before first dose of placebo	17.9±7.0

* Plus–minus values are means ±SD. NALL denotes *N*-acetyl-L-leucine.
† Race or ethnic group was reported by the patients or their representatives.
‡ Duration of disease was calculated as the difference in days between the date of visit 1 and the date of disease onset plus 1; the difference was then converted to months. Disease onset was defined as the earliest of two dates — the date when the disease was first recorded in the patient's medical history or the date of genetic confirmation of the disease. Partially missing dates were imputed with the first day of the month, the first month of the year, or both.
§ Miglustat use indicates concurrent miglustat use throughout the duration of the trial.
¶ The mean baseline scores shown were those used in the end-point comparisons of NALL with placebo. One patient who was assigned to receive NALL in period 1 was withdrawn between visit 3 and visit 4 owing to a serious adverse event that was unrelated to trial treatment. The available data obtained while this patient was receiving NALL in period 1 were used in the primary analysis set by means of the last-observation-carried-forward approach. One patient had an adverse event at visit 6. Data from visit 5 were used in the primary end-point analysis according to the last observation carried forward approach. Only reported data were evaluated in the secondary and exploratory analyses; there was no imputation of missing values for these end points. Because the Clinical Global Impression of Improvement (CGI-I) score reflects a change in a patient's status from baseline to the end of period 1, the assumed change from baseline to the end of period 1 was set as 0 (no change) for all the patients.
‖ Total scores on the Scale for the Assessment and Rating of Ataxia (SARA) range 0 to 40, and total scores on the modified SARA (mSARA) range from 0 to 30; on both scales, lower scores indicate better neurologic status. The mean baseline scores are shown for 60 patients before first dose of NALL and for 59 patients before first dose of placebo.
** The Spinocerebellar Ataxia Functional Index (SCAFI) comprises the timed 8-meter walk test, the timed 9-hole peg test with the dominant and nondominant hand, and the number of spoken repetitions of the bisyllabic phrase "PATA" within 10 seconds. Each test was carried out twice, and the values were averaged; the values for the 8-meter walk test and 9-hole peg test were converted from times to rates, and the results are expressed as a composite z score of each test relative to baseline. A positive score of 1 on the SCAFI indicates an improvement of 1 SD relative to baseline, and a score of –1 indicates a deterioration of 1 SD relative to baseline. The mean baseline scores are shown for 59 patients before first dose of NALL and for 58 patients before first dose of placebo.
†† The modified Disability Rating Scale (mDRS) consists of six subdomains (ambulation, manipulation, seizures, language, swallowing, and ocular movements), with the total score for overall neurologic status ranging from 0 (best) from 24 (worst); scores were scaled to a range of 0 to 1. The mean baseline scores are shown for 60 patients before first dose of NALL and for 59 patients before first dose of placebo.
‡‡ Scores on the Niemann–Pick Disease Type C Clinical Severity Scale (NPC-CSS) range from 0 to 54, with 0 indicating the best neurologic status and 54 the worst. The mean baseline scores are shown for 59 patients before first dose of NALL and for 58 patients before first dose of placebo.

difference, –1.28 points; 95% confidence interval [CI], –1.91 to –0.65; P<0.001) (Table 2). The mean change in the mSARA total score was similar to that in the SARA total score (least-squares mean difference, –0.96 points; 95% CI, –1.45 to –0.46). The total scores on the SARA and mSARA for the individual patients at visits 2, 4, and 6 according to active treatment–placebo sequence are provided in Figure 2. Subgroup analyses are shown in Figure 3.

In period 1, the mean change from baseline (visit 2) in the SARA total score among the 30 patients who received placebo was –0.60 points at visit 4. Among the 29 patients who received NALL in period 1 and placebo in period 2, the symptoms had worsened while they were receiving placebo (mean change in the SARA total score from visit 4 [the end of NALL treatment] to visit 6 [after 12 weeks of receiving placebo] was +1.55 points), a finding that reflects a deterioration in neurologic status when treatment with NALL was stopped.

SECONDARY END POINTS

The results for the secondary end points were generally in the same direction as those for the primary end point. The mean differences (NALL vs. placebo) in the changes in scores were –0.6 points (95% CI, –1.1 to –0.1) for the investigator-rated CGI-I; –0.7 points (95% CI, –1.2 to –0.2) for the caregiver-rated CGI-I; –0.5 points (95% CI, –1.1 to 0.1) for the patient-rated CGI-I; –0.029 points (95% CI, –0.048 to –0.010) for the mDRS (mean baseline scores were 0.477±0.124 before

Table 2. Primary, Secondary, and Exploratory End Points.*

End Point	NALL			Placebo			Difference in Change (95% CI)†
	No. of Patients Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	No. of Patients Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	
Primary end point‡							
SARA	59	13.71±7.68	−1.97±2.43	58	15.2±7.27	−0.60±2.39	−1.28 (−1.91 to −0.65)§
mSARA	59	11.37±5.81	−1.66±1.97	58	12.47±5.34	−0.67±1.74	−0.96 (−1.45 to −0.46)
Secondary end points							
CGI-I¶‖							
Investigator-rated	30	3.3±0.9	−0.7	30	3.9±0.9	−0.1	−0.6 (−1.1 to −0.1)
Caregiver-rated	27	3.6±0.9	−0.4	25	4.3±0.9	0.3	−0.7 (−1.2 to 0.2)
Patient-rated	24	3.3±1.0	−0.7	26	3.8±1.1	−0.2	−0.5 (−1.1 to 0.1)
SCAFI	57	−0.17±0.98	0.05±0.27	56	−0.27±0.99	−0.02±0.31	0.07 (−0.0 to 0.15)
mDRS	59	0.447±0.157	−0.030±0.060	58	0.478±0.136	−0.001±0.061	−0.029 (−0.048 to −0.010)
Exploratory end point							
NPC-CSS¶	58	17.6±6.8	−0.3±2.2	58	18.2±6.9	0.1±2.1	−0.5 (−1.2 to 0.2)

* Plus–minus values are means ±SDs.
† The least-squares mean difference (NALL vs. placebo) is given for the SARA and mSARA.
‡ The primary end point was the total score on the SARA. At the request of the Food and Drug Administration, the total score on the mSARA was used as the primary end point in the United States. In Europe, the mSARA total score was an exploratory end point. The last-observation-carried-forward approach was applied for one patient at visit 4 and for another patient at visit 6 for the total scores on the SARA and mSARA.
§ P<0.001, two-sided.
¶ Only reported data were included in the analyses of the CGI-I and the NPC-CSS scores.
‖ The CGI-I score was calculated for period 1 with the use of a paired t-test. The change from baseline is the reported change from a score of 0 (no change).

receipt of the first dose of NALL and 0.475±0.142 before receipt of the first dose of placebo); and 0.07 (95% CI, −0.0 to 0.15) for the SCAFI (mean baseline scores were −0.39±1.04 before receipt of the first dose of NALL and −0.35±1.02 before receipt of the first dose of placebo) (Table 2). Changes in quality of life that were measured with the use of the EQ-5D-5L and EQ-5D-Y are shown in the Supplementary Appendix.

SAFETY

The adverse events that occurred during the two treatment periods are shown in Table S4. A total of 79 adverse events occurred in 36 patients when they were receiving NALL, and 75 events occurred in 30 patients when they were receiving placebo. No adverse events led to premature discontinuation of the trial. No adverse events occurred in more than 10% of patients when they were receiving NALL. Three patients each had 1 adverse event that was assessed by the investigator to be related to NALL (anal incontinence, restless legs, and rosacea). These events were all transient. The incidence of upper respiratory tract infection was higher when the patients were receiving NALL (10%) than when they were receiving placebo (5%). The incidence of falls was lower when the patients were receiving NALL (7%) than when they were receiving placebo (15%). Epilepsy, which is a feature of Niemann–Pick disease type C, occurred once when a patient was receiving NALL.

No serious adverse events occurred that were considered by an investigator to be related to NALL or placebo. One death was due to aspiration pneumonia after a preplanned placement of a percutaneous endoscopic gastrostomy tube and therefore was not related to trial treatment. The results of plasma and urine tests, vital signs, and electrocardiographic recordings were normal or were rated as clinically nonsignificant. Adherence to NALL or placebo was high, as shown by the results of regular urine analyses for prohibited medications.

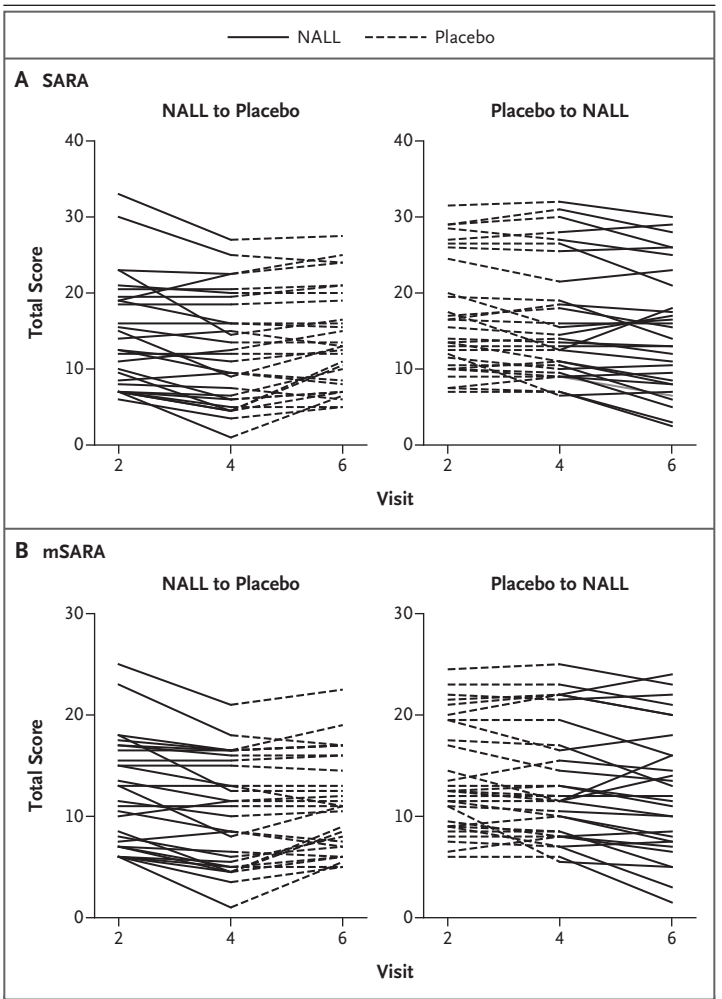

Figure 2. SARA and mSARA Total Scores at Visits 2, 4, and 6.

Shown are the total scores on the Scale for the Assessment and Rating of Ataxia (SARA; Panel A) and the modified SARA (mSARA; Panel B) for the individual patients at visits 2, 4, and 6 according to active treatment–placebo treatment. Total scores on the SARA range from 0 to 40, and total scores on the mSARA range from 0 to 30; on both scales, lower scores indicate better neurologic status.

DISCUSSION

In this trial, patients with Niemann–Pick type C had a significant reduction in neurologic signs and symptoms during the period they were receiving NALL, as compared with the period they were receiving placebo, with a difference of –1.28 points in the change in score from baseline on a 40-point scale used to assess the severity of neurologic status in multiple domains. The deterioration in neurologic status when the patients were receiving placebo, after having crossed over from NALL treatment, suggests that treatment with NALL has an effect on symptoms. However, such deterioration does not establish whether there was a fundamental biologic effect on the disease. The findings from this phase 3 trial are consistent with those of a previous phase 2b trial involving pediatric and adult patients with

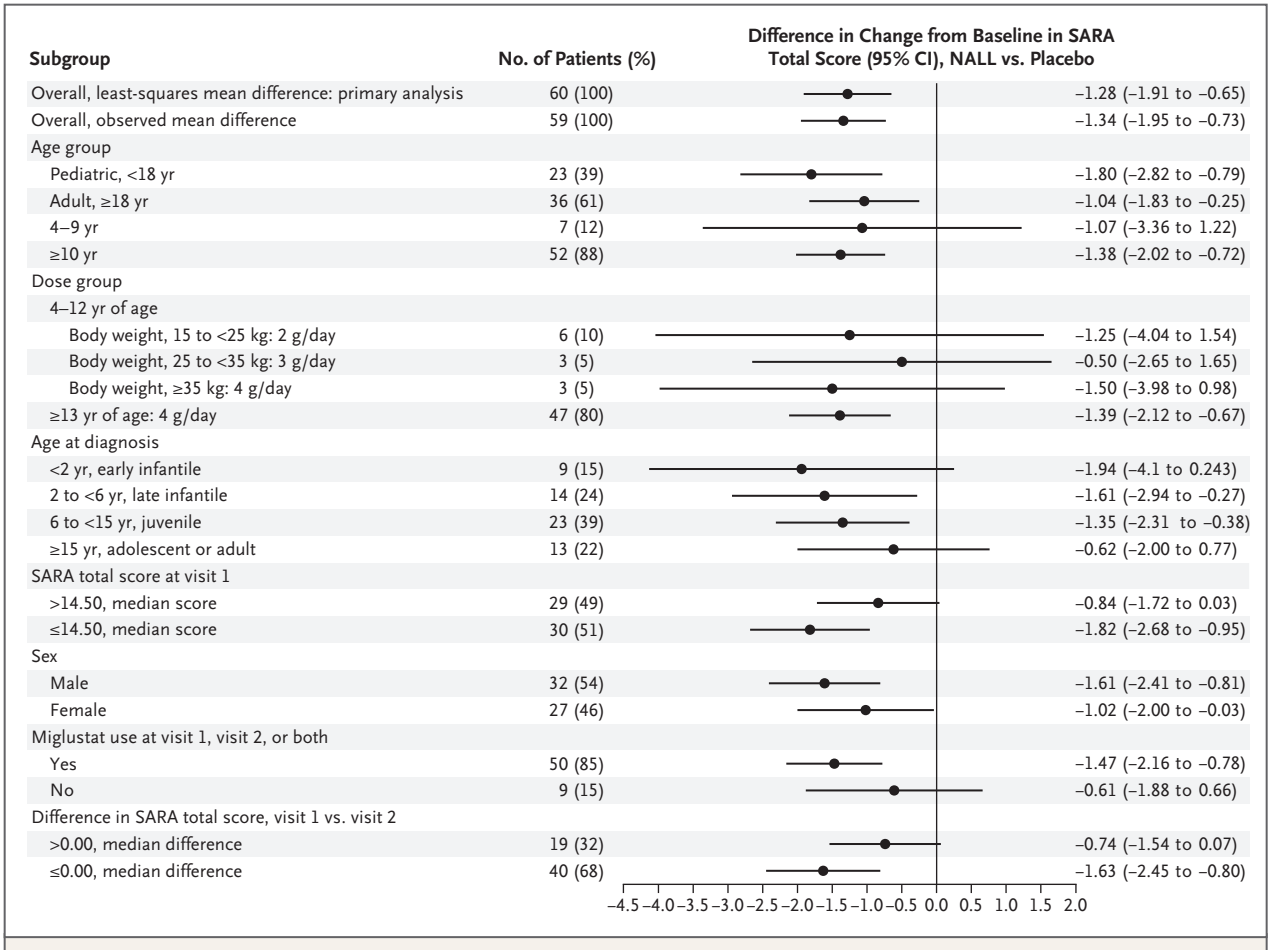

Figure 3. Overall and Subgroup Analyses of the Change from Baseline in the SARA Total Score.

In the overall analyses, the least-squares mean difference was determined with the use of the mixed-effects model, which included data from all 60 patients, and the observed mean difference was determined with data from the 59 patients who completed both visit 4 in period 1 and visit 6 in period 2. Data from these 59 patients were also used in each subgroup analysis.

Niemann–Pick disease type C, which showed that scores on the SARA, mSARA, and CGI-I improved with NALL treatment but subsequently worsened in the post-treatment washout period.[10] There was also a low incidence of treatment-related adverse events.

Our trial has several limitations, the first of which was the 12-week duration of active treatment. The trial was designed to investigate the symptomatic effects of NALL; data from the ongoing extension phase of the trial should provide further insight into the possible effect of NALL treatment on disease progression and the incidence of adverse events. Second, the focus on symptomatic end points led to the exclusion of patients younger than 4 years of age, asymptomatic patients, or patients with advanced disease who would not be able, or reliably able, to complete functional assessments. The SARA has been validated for use in patients with variants of spinocerebellar ataxia and has not been formally validated for use in patients with Niemann–Pick disease type C. Finally, there is no validated biomarker for Niemann–Pick disease type C or surrogate end point that is indicative of clinical improvement.

In this phase 3 trial involving patients with Niemann–Pick disease type C, treatment with NALL reduced neurologic signs and symptoms as compared with placebo over 12 weeks. Larger and longer studies are required to determine the long-term effect of this agent in patients with Niemann–Pick disease type C.

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APPENDIX

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