Efficacy Confirmation Study of Aceneuramic Acid Administration for GNE Myopathy in Japan

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Abstract

Background

A rare muscle disease, GNE myopathy is caused by mutations in the GNE gene involved in the sialic acid biosynthesis. Our recent phase II/III study has indicated that oral administration of aceneuramic acid to patients would slow disease progression.

Methods

We conducted a phase III, randomized, placebo-controlled, double-blind, parallel-group, multicenter study. Participants were assigned to receive an extended-release formulation of aceneuramic acid (SA-ER) or placebo. Changes in muscle strength and function over 48 weeks were compared between treatment groups using change in the upper extremity composite (UEC) score from baseline to Week 48 as the primary endpoint and the investigator-assessed efficacy rate as the key secondary endpoint. For safety, adverse events, vital signs, body weight, electrocardiogram, and clinical laboratory results were monitored.

Results

A total of 14 patients were enrolled and given orally SA-ER (n = 10) or placebo (n = 4) tablets. Decrease in least square mean (LSM) of change in UEC score at Week 48 with SA-ER (-0.115 kg) was numerically smaller as compared with placebo (-2.625 kg), with LSM difference (95% confidence interval) of 2.510 (-1.720 to 6.740) kg. In addition, efficacy rate was higher with SA-ER as compared with placebo. There were no clinically significant adverse events and other safety concerns observed.

Conclusions

The present study reproducibly showed the effect of orally administered SA-ER on slowing loss of muscle strength and function, indicating supplementation of sialic acid might be a promising replacement therapy for GNE myopathy.

Trial registration number: ClinicalTrials.gov (NCT04671472)

INTRODUCTION

GNE myopathy (also known as distal myopathy with rimmed vacuoles [DMRV], hereditary inclusion body myopathy [hIBM] or Nonaka Disease) is a hereditary myogenic disorder that develops muscle weakness due to defect in muscle itself [1–6]. Although most of the myogenic disorders present with affected muscles in trunk (around chest and hip) as well as upper arms and thigh proximal to trunk, the distal myopathy has a characteristic of gradually-progressing weakness of muscles from distal part of arms and legs, particularly such as fingers and lower legs. GNE myopathy is also known as an ultra-orphan
disease; the estimated number of patients are 150–400 in Japan and 40,000 in the world [4, 7]. Most patients with GNE myopathy present with manifestations at ages ranging from 15 to 35 [8].

Previously, the onset mechanism of GNE myopathy remained fully unknown. In 2001, Eisenberg et al. identified missense mutations in the GNE gene in patients with GNE myopathy [9]. The GNE gene encodes UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE/MNK) [10], the rate-limiting enzyme in the biosynthetic pathway of sialic acid. This finding suggested that sialic acid required for muscle function is insufficiently supplied in the body of the patients due to defect in its biosynthesis, and that replacement of sialic acid is a potential therapy to improve the pathology of GNE myopathy [11]. Accordingly, the efficacy of the replacement therapy was assessed in a GNE myopathy mouse model [12] established in the National Center of Neurology and Psychiatry (NCNP) in Japan. Continuous administration of aceneuramic acid to the model mice prior to disease onset allowed for comparable motor performance, contractile strength of skeletal muscles, biochemical parameters, and muscle pathological features over time to normal mice [13]. This non-clinical study suggested that oral supplementation of aceneuramic acid could be expected to improve the pathological conditions and slow disease progression in patients with GNE myopathy.

To evaluate the safety and pharmacokinetics of orally administered aceneuramic acid in humans, we conducted phase I studies in GNE myopathy patients [14] and observed the elevated levels of serum free aceneuramic acid with no safety issues using an extended-release formulation of aceneuramic acid (SA-ER). The results were consistent with those of a prior international phase II study [15]. In our recent phase II/III study in Japan (UMIN 000020683), the primary endpoint was change in the upper extremity composite (UEC) score (mean ± standard deviation [SD]), which was as small as −0.08 ± 3.70 kg in the SA-ER group vs. −5.08 ± 3.38 kg in the placebo group [16]. The differences between the two groups were statistically significant or nearly significant with consistency when analyzed by several statistical methods. There were no adverse events that would pose safety concerns. In the United States, an international double-blind phase III study evaluating the efficacy and safety of SA-ER for 48 weeks was conducted in GNE myopathy patients from 7 countries. However, this study failed to achieve significant difference between the SA-ER group and the placebo group for the primary endpoint, UEC score [17].

GNE myopathy is a rare disease that gradually progresses over a long time [5, 6, 18–20]. Further, recent studies have suggested that natural history of the disease may vary depending on patient backgrounds [19, 20]. Therefore, it is a challenge to clarify if replacement of sialic acid as a medical treatment would slow progression of and improve symptoms of the disease. In the present phase III study, we focused on a subset limited by GNE myopathy-Functional Activity Scale (GNEM-FAS) score and disease duration to minimize variation in patient backgrounds and indicated the reproducible efficacy of sialic acid supplementation in patients with GNE myopathy.

**METHODS**

**Study design**
This was a phase III, randomized, placebo-controlled, double-blind, parallel-group, multicenter study conducted at five sites in Japan (Department of Neurology at Tohoku University Hospital, National Center Hospital, NCNP; Nagoya University Hospital; Osaka University Hospital; and Kumamoto University Hospital), in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and study protocol. This study was reviewed in terms of ethical, scientific, and medical validity and approved by the institutional review board at each site before the start of the study. Duration of the study was between Feb 8, 2021 and March 29, 2022. The study is registered on ClinicalTrials.gov (NCT04671472).

Participants

The key inclusion criteria for participating in this study included: confirmed mutations in the GNE gene and documented diagnosis of GNE myopathy; aged 20 years or more to 50 years or less at the time of consent acquisition; a score of 24 points or more on the upper extremity of GNEM-FAS and a disease period of 5 years or more and 15 years or less; those whose muscle weakness of upper extremity had been confirmed from the results of manual muscle testing (MMT) or grip strength measurements over the past several years, or if had participated in our previous phase II/III study, those who was able to confirm UEC score decreased during non-treatment period; and those who was able to provide reproducible force in elbow extensors/flexors (i.e., two dynamometry force values with less than 15% variability in the dominant arm) at screening. The key exclusion criteria included: use of N-acetyl-D-mannosamine (ManNAc), sialic acid (ex., aceneuramic acid), or related metabolites, intravenous immunoglobulin (IVIG), or anything that can be metabolized to produce sialic acid in the body within 60 days before screening; hypersensitivity to aceneuramic acid or its excipients; and liver function test (i.e., aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase) levels greater than 3X the upper limit of normal (ULN) for age/gender, or serum creatinine of greater than 2X ULN at screening.

Randomization and intervention

Participants were randomly assigned in a 7:3 ratio to the SA-ER group and the placebo group, and all participants received either treatment. As our recent phase II/III study, the investigational products used were a SA-ER tablet containing 500 mg of aceneuramic acid and a matching placebo tablet. Participants were administered orally four SA-ER or placebo tablets three times per day (6 g/day), in the morning, early evening, and at bedtime after meal (within 30 min after intake of meal or right meal).

Outcomes

Participants were subjected to the following efficacy assessments every 12 weeks over 48 weeks. The primary endpoint was change in UEC score from baseline to Week 48. UEC score was calculated as the sum of bilateral average of strength values (in kilograms) for grip, shoulder abductors, elbow flexors, and elbow extensors. Each muscle strength was measured with a hand-held dynamometer.

The key secondary endpoint was efficacy rate in comprehensive assessment by the investigator. First, the investigator assessed the following 4 items by any of improvement, immutability, deterioration, and
undecidable (not applicable): (1) MMT for upper extremity, or grip strength, (2) UEC score, (3) change in UEC score compared with the placebo-administered GNE myopathy patients in previous clinical studies, and (4) other secondary endpoints. Subsequently, the comprehensive efficacy in each patient was assessed as effective, ineffective, or undeterminable by integrating the assessments (1) – (4).

Other secondary endpoints included the following change from baseline to Week 48: GNEM-FAS upper extremity, mobility, and self-care scores; GNEM-FAS total score; bilateral average of individual muscle strength for grip, shoulder abductors, elbow flexors, and elbow extensors comprising UEC score; bilateral average of muscle strength for knee extensors.

The safety assessments included the incidence and severity of adverse events, vital signs and weight, electrocardiogram, and clinical laboratory tests.

**Serum free and total aceneuramic acid concentration**

Methods for blood sampling and determination of serum free and total aceneuramic acid concentrations were performed according to those described in the previous study [14]. Serum free and total aceneuramic acid concentrations (µg/mL) were measured at baseline and every 12 weeks before administration (trough concentration).

**Sample size**

According to data from the Registry of Muscular Dystrophy (REMUDY, http://www.remudy.jp/) [18], a registry system of patients with neuromuscular disease in Japan, the number of subjects included in this study was presumed to be not significantly different from that estimated at our previous phase II/III study in Japan. In the present study, eligible participants were required to meet additional inclusion criteria: (a) those who had a score of 24 points or more on the upper extremity of GNEM-FAS and a disease period of 5 to 15 years, and (b) those whose upper extremity muscle weakness had been confirmed from the results of MMT or grip strength measurements over the past few years, or if had participated in our previous phase II/III study, those who was able to confirm UEC score decreased during non-treatment period. Fourteen of 19 participants in the previous study met the criteria (a). Based on the current examination of the number of patients in the REMUDY and the five sites that had participated in the previous study, 28 patients were presumed to meet the inclusion criteria of the previous study. Accordingly, patients that would meet the inclusion criteria in the present study was estimated to be 21 (= 28 x 14/19). Further, given another criterion, “muscle weakness had been confirmed over the past few years prior the present study” and the possibility of less participants in placebo-controlled studies, feasible target sample size was estimated to be 10-15 patients. This estimation included patients that had participated in the previous study; hence, newly enrolled patients in the present study were set to be 5 or more.

**Statistical analysis**
SAS software version 9.4 (SAS Institute Japan Ltd.) was used for statistical analyses. The following efficacy analyses were performed in full analysis set (FAS) that included all the enrolled participants except for those with screening failure, no administration of study drug, or no efficacy data after starting study treatment. **Primary endpoint:** for statistical analysis of change in UEC score from baseline to Week 48, we first constructed a linear mixed effect model including change from baseline as an objective variable, visit, treatment group and interaction of visit*treatment group as fixed effects, and subject as random effect. Using this model in consideration of intra-subject correlation, we estimated least square mean (LSM) of UEC change as well as between-group difference in LSM of UEC change and its 95% confidence interval [CI] by visit (Week 12, Week 24, Week 36, and Week 48). We also calculated mean ± SD in change of UEC score by treatment group and visit, and further provided its transition diagram over time by treatment group. **Key secondary endpoint:** efficacy rate and its 95% CI for investigator-integrated efficacy assessment were estimated by treatment in FAS. **Other secondary endpoints:** mean ± SD of change from baseline in each measurement was estimated by treatment group and visit, and its transition diagram over time was provided. For serum free and total aceneuramic acid concentrations, mean ± SD of measurement by treatment group and visit was calculated and its transition diagram over time was presented.

Safety assessments were performed in safety population that included all the participants who received an investigational drug and provided any safety data. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 25.0.

Further details on the Methods can be found in the full protocol provided in the supplementary materials.

**RESULTS**

**Baseline characteristics and disposition of patients**

A total of 14 patients were enrolled and randomly assigned to the SA-ER group (10 subjects) or the placebo group (4 subjects). All the participants in both groups received the assigned investigational agent for 48 weeks, completed the follow-up examination 4 weeks after the last administration, and included in FAS for efficacy assessments and safety population for safety assessments. There was no participant leading to discontinuation of the study.

Table 1 shows baseline demographic and clinical characteristics of the patients. The median age of all the patients was 40.5 years and 4 patients (28.6%) were male. Overall, baseline characteristics including UEC score and GNEM-FAS upper extremity score were generally balanced between treatment groups.

**Outcomes**

**Serum concentration of aceneuramic acid**

Serum free aceneuramic acid concentration almost unchanged over time in the placebo group but clearly increased approximately 2-fold in the SA-ER group after Week 12 (Figure 1). In contrast, serum total...
aceneuramic acid concentration did not change largely in both groups.

**Efficacy evaluations**

**Primary endpoint**

Figure 2 illustrates change in UEC score from baseline to Week 48 in both groups. Decline in UEC score in the SA-ER group during 48 weeks of treatment appeared to be suppressed compared to the placebo group. We then constructed a linear mixed effect model to analyze the difference between the two groups. As shown in Table 2, decrease in LSM of change in UEC score at Week 48 was numerically smaller in the SA-ER group (−0.115 kg) than in the placebo group (−2.625 kg), with LSM difference (95% CI) between the two groups of 2.510 (−1.720 to 6.740) kg.

**Key secondary endpoint**

For the investigator-assessed efficacy rate, 7 of 10 subjects in the SA-ER group and 2 of 4 subjects in the placebo group were assessed as “effective.” A higher efficacy rate was noted with SA-ER (70%, 95% CI: 34.75 to 93.33) as compared with placebo (50%, 95% CI: 6.76 to 93.24) (Table 3).

**Other secondary endpoints**

GNEM-FAS upper extremity score did not change remarkably until Week 36 and slightly decreased at Week 48 in the SA-ER group, while clearly declined at Week 12 and later in the placebo group (Figure 3). GNEM-FAS mobility score did not change obviously over 48 weeks in the SA-ER group but apparently declined at Week 24 and later in the placebo group (Figure 4a). GNEM-FAS self-care score did not change largely in both groups (Figure 4b). GNEM-FAS total score exhibited similar pattern to GNEM-FAS upper extremity score (Figure 4c). For individual muscle strength for grip, shoulder abductors, elbow flexors, and elbow extensors comprising UEC score, decline in the placebo group was not clear except for grip strength; any of muscle strengths in the SA-ER group remained unchanged (Supplementary Figure 1). Knee extensor strength as a measurement of lower extremity remained relatively spared in both groups over 48 weeks (Supplementary Figure 2).

**Safety assessment**

The number and incidence rate of adverse events reported were 55 events and 90% (9/10 subjects) in the SA-ER group, and 17 events and 100% (4/4 subjects) in the placebo group, respectively (Table 4). Serious adverse events reported were one event of COVID-19 in one subject in the SA-ER group and one event of papillary thyroid cancer in one subject in the placebo group (see Supplementary Table 1 for full adverse events). Both events were considered unrelated to study drug. There were no death and no adverse event leading to discontinuation of study in both groups. Adverse events observed in two or more subjects of the SA-ER group were: dry eye, diarrhoea, gastrooesophageal reflux disease, pyrexia, immunisation reaction, and nasopharyngitis. Of these, diarrhoea, pyrexia, immunisation reaction, and nasopharyngitis were also reported in the placebo group. All immunisation reaction events were side reactions caused by
vaccination for Coronavirus COVID-19. Serious adverse events were only two events above and all the other events were mild or moderate in severity. For gastrointestinal disorders, there were 19 events in 6 subjects in the SA-ER group and 5 events in 2 subjects in the placebo group. For musculoskeletal and connective tissue disorders, there were 8 events in 2 subjects in the SA-ER group and no event in the placebo group. Both disorders were reported more commonly with SA-ER as compared with placebo. No adverse events were considered study drug-related.

DISCUSSION

GNE myopathy is an orphan muscle disorder for which no treatment has been approved in the world. Recently, we conducted a phase II/III study to evaluate the efficacy and safety of orally administered SA-ER in patients and showed a significantly higher UEC score at Week 48 in the SA-ER group compared to that in the placebo group with no safety issues. The aim of the present phase III study was to confirm the efficacy and safety of SA-ER in patients with GNE myopathy.

Consistent with observations from our previous phase I and phase II/III studies, and other clinical studies [14, 15, 17], we confirmed an obvious increase in serum free aceneuramic acid concentration after oral administration of SA-ER 6 g/day over 48 weeks, which indicated that orally administered aceneuramic acid was efficiently absorbed into the body and utilized in tissues.

In the present study, the primary endpoint was change in UEC score at Week 48, which was also employed as the primary endpoint in the international phase III study [17] and our recent phase II/III study [16], both dosing SA-ER. Decrease in UEC score at Week 48 was numerically smaller in the SA-ER group than in the placebo group, thus indicating that oral administration of SA-ER 6 g/day but not placebo to patients with GNE myopathy might have maintained their muscle strengths as measured by UEC score during 48 weeks of treatment. This finding implied a trend toward a treatment benefit of SA-ER as compared with placebo. Subsequently, we performed a post hoc efficacy analysis using combined data of subjects in our recent phase II/III study [16] and newly enrolled subjects in the present phase III study, which showed statistically significant efficacy of SA-ER as compared with placebo (Supplementary Table 2). In addition, the result of investigator-assessed efficacy rate also favored the effect of SA-ER on slowing disease progression. GNEM-FAS was developed to assess functional conditions specifically in GNE myopathy patients and used in previous aceneuramic acid supplementation studies [15, 17]. In our present study, plots of GNEM-FAS upper extremity and mobility scores separated from each other between the SA-ER group and the placebo group, indicating the effect of oral SA-ER on counteracting loss of muscle function. A similar plot separation was also observed in GNEM-FAS total score, reflecting the changes in upper extremity and mobility scores. Finally, knee extensor strength appeared stable over 48 weeks, probably due to quadriceps-sparing nature of GNE myopathy [2, 8, 15].

Previously, the efficacy of SA-ER administration to patients with GNE myopathy has been observed in the international phase II study [15] and our recent phase II/III study [16]. However, the international phase III study could not show a benefit of SA-ER as compared with placebo [17]. With regard to this, we assumed
that the effect of SA-ER could be affected in part by degree of disease progression at baseline. GNEMFAS score assesses functional conditions in GNE myopathy patients and appears to reflect progression of the disease more properly than muscle strength. With data of the previous clinical studies including the international phase III study, we attempted to identify a subgroup showing the efficacy of SA-ER by confining baseline GNEM-FAS upper extremity score. Duration of disease was also considered because patients with shorter disease duration are difficult to assess decline in muscle function and patients with longer disease duration are unlikely to be under disease progression thereafter. Finally, when focusing on a subgroup of patients who had GNEM-FAS upper extremity score of 24 points or more and a disease duration of 5 years or more and 15 years or less, we noted significant efficacy (in change in UEC score) of SA-ER as compared with placebo in patients from the international phase II and phase III studies and our recent phase II/III study [16]. Based on this result, we conducted the present study with patients meeting the above criteria and confirmed a clinical benefit of SA-ER, which suggests the importance of wellpreserved muscle function and disease duration for efficacy evaluation of SA-ER treatment.

For safety, most of the adverse events were mild or moderate in severity. Two serious adverse events were reported but considered study drug-unrelated. Thus, the safety profile of SA-ER is considered acceptable, which is consistent with previous phase I studies [14].

The present study has some limitations. First, owing to the rarity of GNE myopathy, a limited number of patients participated in the study. Moreover, we added some inclusion criteria to minimize background variation in study population. It may affect statistical power to detect the difference between treatment groups. Second, progress of GNE myopathy generally takes long time and varies among individuals in the natural history. Despite relatively homogeneous study population as above, muscle strength and function might not have declined in a similar manner in the absence of aceneuramic acid among participants during 48 weeks of treatment. Further, long-term efficacy of SA-ER was not evaluated in the present study, although a long-term (72 weeks) extension study following our previous phase II/III study shows preservation of muscle strength (unpublished). Finally, only patients with mild symptoms (GNEM-FAS upper extremity score of 24 or more) were included in this study. It should be evaluated in future studies whether oral SA-ER is effective for patients with more severe symptoms.

In summary, the present phase III study in patients with GNE myopathy indicated a clinical benefit of orally administered SA-ER (6 g/day), with no safety concerns. Combined with our recent phase II/III study, oral aceneuramic acid is considered a promising therapeutic agent for mild GNE myopathy.

CONCLUSIONS

The present study reproducibly showed the effect of orally administered SA-ER on slowing loss of muscle strength and function, indicating supplementation of sialic acid might be a promising replacement therapy for GNE myopathy.

Declarations
Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tohoku University Hospital. All patients gave informed, written consent to participate.

Consent for publication

All study subjects provided written informed consent.

Availability of data and materials

All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Competing interests

The authors declare that they have no competing financial interests.

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Authors’ Contributors

NS, IN, and MA designed the study. MMY, NS, MasahisaK, MPT, SaY, YO, AH, ShY, MN, MasaakiK, RI, MK, HW, MT, HK acquired the data. RA, TY, and IN contributed to data quality assurance and data quality analysis. NS, RI, and MA analyzed the data. NS, and MA drafted the manuscript. All authors revised the manuscript and gave final approval for publication.

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References


**Tables**

Tables 1 to 4 are available in the Supplementary Files section.

**Figures**
Figure 1

(a) Mean and SD plots in serum free (a) and total (b) aceneuramic acid levels (FAS). Blood sampling and determination of serum free/total aceneuramic acid concentrations were performed as described previously [14]. FAS, full analysis set; SA-ER, sialic acid extended-release; SD, standard deviation.
Figure 2

Mean and SD plots in change from baseline in UEC score (FAS). Grip strength of 4 kg or less treated as 0 kg. FAS, full analysis set; SA-ER, sialic acid extended-release; SD, standard deviation; UEC, upper extremity composite.
Figure 3

Mean and SD plots in change from baseline in GNEM-FAS upper extremity score (FAS). FAS, full analysis set; GNEM-FAS, GNE myopathy-Functional Activity Scale; SA-ER, sialic acid extended-release; SD, standard deviation.
Figure 4

Mean and SD plots in change from baseline in other scores of GNEM-FAS (FAS). (a) mobility score, (b) self-care score, and (c) total score. FAS, full analysis set; GNEM-FAS, GNE myopathy-Functional Activity Scale; SA-ER, sialic acid extended-release; SD, standard deviation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 230429GNEmyopathyConfirmationpaperTables.pdf
- 230502GNEmyopathyConfirmationpaperSuppleFigsTables.pdf