Report on the Deliberation Results

March 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Acenobel Extended Release Tablets 500 mg
Non-proprietary Name	Aceneuramic Acid (JAN*)
Applicant	Nobelpharma Co., Ltd.
Date of Application	July 26, 2023

Results of Deliberation

In its meeting held on February 29, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered, to understand the characteristics of patients using the product. The applicant is also required to promptly collect data on the safety and efficacy of the product so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

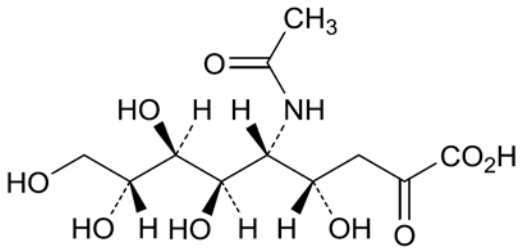
Review Report

February 21, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Acenobel Extended Release Tablets 500 mg
Non-proprietary Name	Aceneuramic Acid
Applicant	Nobelpharma Co., Ltd.
Date of Application	July 26, 2023
Dosage Form/Strength	Extended release tablets: Each tablet contains 500 mg of aceneuramic acid.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{11}H_{19}NO_9$
Molecular weight: 309.27
Chemical name: (4*S*,5*R*,6*R*,7*S*,8*R*)-5-Acetamido-4,6,7,8,9-pentahydroxy-2-oxononanoic acid

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 501 of 2021 [*R3 yaku*]; PSEHB/PED Notification No. 0219-1 dated February 19, 2021, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in suppressing the progression of muscular weakness in patients with distal myopathy with rimmed vacuoles, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions.

Indication

Suppression of the progression of muscular weakness in patients with distal myopathy with rimmed vacuoles

Dosage and Administration

The usual adult dosage is 2 g of aceneuramic acid orally administered 3 times daily after meals, approximately 8 hours apart.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered, to understand the characteristics of patients using the product. The applicant is also required to promptly collect data on the safety and efficacy of the product so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

January 25, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Acenobel Extended Release Tablets 500 mg
Non-proprietary Name	Aceneuramic Acid
Applicant	Nobelpharma Co., Ltd.
Date of Application	July 26, 2023
Dosage Form/Strength	Extended release tablets: Each tablet contains 500 mg of aceneuramic acid.
Proposed Indication	Suppression of the progression of muscular weakness in patients with GNE myopathy

Proposed Dosage and Administration

The usual adult dosage is 2 g of aceneuramic acid orally administered 3 times daily after meals. The dose may be reduced according to the patient's condition.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

GNE myopathy is an autosomal recessive disease that is caused by mutations in the *GNE* gene encoding UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE/MNK) that is the key enzyme involved in the biosynthesis of sialic acid, a type of carbohydrate present in the human body. The mutation reduces the biosynthesis of sialic acids including aceneuramic acid, leading to the onset of the disease (*Nat Genet.* 2001;29:83-7). GNE myopathy is also known as distal myopathy with rimmed vacuoles (DMRV), hereditary inclusion body myopathy, and Nonaka disease.

DMRV is a type of "distal myopathy," a designated intractable disease, primarily characterized by the atrophy of muscle tissue and degeneration of muscle fibers. The pathological features of affected muscles include rimmed vacuoles, atrophic angulated fibers (*Ann Neurol.* 1985;17:51-9), and amyloid deposits within muscle fibers (*Acta Neuropathol.* 1995;89:29-34). The disease usually develops in people in their late teens to 30s. Flexor femoris muscle, adductor muscle of the thigh, abductor muscle of the thigh, and anterior tibial muscle in the lower limbs are affected earlier than the upper limb muscles, and the progression of muscle weakness is rapid. If the muscles throughout the entire lower leg (below the knee) are affected, it may result in difficulty walking. The mean duration from disease onset to reach specific disease stage (assistive device use, wheelchair use, and loss of ambulation) in patients with DMRV has been reported to be 12, 15, and 21 years, respectively (*Orphanet J Rare Dis.* 2014;9:150). Muscle weakness in the upper limb gradually progresses from the fingers to the entire upper limb. As muscle strength declines, constant assistance in daily activities of living gradually becomes necessary for the patients. Severely affected patients may become bedridden. An estimated number of patients with DMRV in Japan ranges from 167 to 345 (FY2009 Report, "Estimation of the number of patients with each type of distal myopathy in Japan and genetic diagnosis of DMRV [in Japanese]," Research Project on Rare and Intractable Diseases, funded by Health and Labour Sciences Research Grants).

The primary treatment for DMRV is rehabilitation aimed at preventing contracture. In recent years, the medical device "Biosignal-responsive motor function improvement device" (brand name, HAL for Medical Use [Lower Limb Type]) has also been used for rehabilitation, whereas no drugs have been approved for the treatment of DMRV in Japan.

Acenobel Extended Release Tablets 500 mg (Acenobel) is an oral drug containing aceneuramic acid, a type of sialic acid, as the active ingredient. It is expected to be effective in suppressing the progression of muscle weakness in patients with DMRV by supplementing sialic acid that is deficient in patients with DMRV.

For the development of aceneuramic acid for DMRV, an investigator-initiated clinical study was started in Japan in November 2010. The applicant has submitted an application for marketing approval based on the results of clinical studies, including the investigator-initiated clinical study.

The Japanese phase I studies (CTD 5.3.3.2-1, Sialic Acid-1 study and CTD 5.3.3.2-2, Sialic Acid-2 study), the Japanese phase III study (1) (CTD 5.3.5.1-1, Sialic Acid-3 study), and the Japanese long-term treatment study (CTD 5.3.5.2-1, Sialic Acid-4 study) were conducted with support programs

by the New Energy and Industrial Technology Development Organization (NEDO); the Japan Science and Technology Agency (JST); the Ministry of Health, Labour and Welfare; the Ministry of Education, Culture, Sports, Science and Technology; and the Japan Agency for Medical Research and Development (AMED).[1)]

Aceneuramic acid has been designated as an orphan drug for the intended indication of "Suppression of the progression of muscular weakness in patients with GNE myopathy" (Orphan Drug Designation No. 501 of 2021 [*R3 yaku*]; PSEHB/PED Notification 0219-1 dated February 19, 2021).

As of December 2023, aceneuramic acid is not approved in any foreign country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. The determined general properties include description, solubility, melting point, dissociation constant, specific rotation, hygroscopicity, and polymorphism. The drug substance exists in 5 different crystalline forms (Forms 1 to 5), but it has been confirmed that only Form 1 ([redacted]) is produced in the commercial manufacturing process.

The chemical structure of the drug substance was elucidated by nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), electrospray ionization-mass spectrometry (ESI-MS), X-ray powder diffraction, and infrared absorption spectroscopy (IR).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as the starting materials.

[redacted] and [redacted], [redacted], and [redacted] were identified as the critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, high performance liquid chromatography [HPLC]), specific optical rotation, purity (related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, and assay (HPLC).

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1) Japanese phase I study (CTD 5.3.3.2-1: Sialic Acid-1 study): "Project to Promote the Practical Application of Innovative Technology in Fiscal 2009 (in Japanese)" (NEDO) and "Adaptable and Seamless Technology Transfer Program through Target-driven R&D, Full-scale R&D Stage, High-Risk Challenge Type" (JST).
Japanese phase I study (CTD 5.3.3.2-2: Sialic Acid-2 study): "Translational Research Network Program," funded by Grant-in-Aid for Shared Facilities and Promotion of Inter-Institutional Collaborative Research (Ministry of Education, Culture, Sports, Science and Technology) and "Research Project on Rare and Intractable Diseases (Intractable Diseases Research Project)," funded by Health and Labour Sciences Research Grants (Ministry of Health, Labour and Welfare)
Japanese phase III study (1) (CTD 5.3.5.1-1: Sialic Acid-3 study) and Japanese long-term treatment study (CTD 5.3.5.2-1: Sialic Acid-4 study): Practical Research Project for Rare/Intractable Diseases (AMED) and Project Promoting Support for Drug Discovery/Support Program for Orphan Drugs prior to the Designation (AMED)

2.1.4 Stability of drug substance

Table 1 shows main stability studies conducted on the drug substance. Results confirmed that the drug substance is stable. A photostability testing showed that the drug substance is photo-stable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage containers	Storage period
Long-term	3 commercial-scale batches	5 ± 3°C	-	Polyethylene bag (double-layered) with desiccant + aluminum bag (heat-sealed)	24 months
Accelerated		25 ± 2°C	60 ± 5% RH		6 months

Based on the above, a retest period of 24 months has been proposed for the drug substance when stored at 2°C to 8°C in the polyethylene bag placed in another polyethylene bag with desiccant and in an aluminum bag (heat-sealed). The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product comes as extended-release tablets, each containing 500 mg of aceneuramic acid. The excipients contained in the drug product are hypromellose, sodium alginate, carrageenan, silicified microcrystalline cellulose, and magnesium stearate.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising mixing/granulation/drying, lubricant mixing, tableting, packaging/labeling, and testing/storage. [redacted] and [redacted] were identified as the critical steps. In-process control parameters and control values have been established for the mixing/granulation/drying, lubricant mixing, tableting, and packaging/labeling processes.

The quality control strategy was designed based on the following investigations (Table 2):

- Identification of critical quality attributes (CQAs)
- Quality risk assessment

Table 2. Summary of control strategy for drug product

CQA	Control method
Strength	Specifications
Description	Specifications
Identification	Specifications
Purity, related substances	Specifications
Uniformity of dosage unit	Manufacturing process and specifications
Dissolution	Specifications
Microbial limit	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (ultraviolet-visible spectroscopy [UV/VIS]), purity (related substances [HPLC]), water content, uniformity of dosage units (mass variation), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 3 shows the main stability studies conducted on the drug product. The drug product was stable under the long-term testing condition, whereas a tendency toward an increase over time in multiple

related substances was observed in the accelerated testing condition. A tendency toward an increase over time in multiple related substances was also noted in the intermediate testing condition.

Table 3. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage containers	Storage period
Long-term	3 pilot scale batches	25 ± 2°C	60 ± 5%RH	Polyethylene bottle with polypropylene cap	24 months
Intermediate	1 pilot scale batch	30 ± 2°C	65 ± 5%RH		12 months
Accelerated	3 pilot scale batches	40 ± 2°C	75 ± 5%RH		6 months

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is generally adequately controlled. As described in Sections 2.R.2 and 2.R.3, PMDA will finalize the appropriateness of the above conclusion in the Review Report (2), taking account of the results of the ongoing photostability testing for the drug product and of the validation of analytical procedures for the drug substance.

2.R.1 Shelf-life of drug product

PMDA asked the applicant to justify the appropriateness of the proposed shelf-life of the drug product, based on the results of the stability studies conducted.

The applicant's explanation:

The intermediate stability study for up to 12 months showed a tendency toward an increase over time in multiple related substances, whereas the stability of the drug product was demonstrated in the long-term stability study for up to 24 months. The applicant therefore considered that the shelf-life of 24 months should be selected for the drug product filled in a polyethylene bottle with a polypropylene cap and placed in a paper box and stored at room temperature (1°C to 30°C). However, the stability studies of the drug product (long-term, intermediate, and accelerated studies) showed a clear tendency toward an increase in multiple related substances with a rise in the storage temperature. A focus was placed on the results of the intermediate study in establishing the shelf-life of the drug product stored at room temperature. The drug product was predicted to be stable up to 20 months, according to the results of the regression analysis of the data up to 12 months of the intermediate study. The applicant considered that the shelf-life of 20 months should be selected for the drug product stored at room temperature, filled in a polyethylene bottle with a polypropylene cap and placed in a paper box. Since the intermediate study was conducted using only 1 batch of the drug product, an additional intermediate study up to 24 months will be conducted using 3 commercial-scale batches of the drug product. When the results of the study at 20 months becomes available, the shelf-life of the drug product will be validated.

PMDA's view:

The results of the stability studies of the drug product (long-term, intermediate, and accelerated studies) indicated that the extent of the increase over time in multiple related substances tends to become greater with increasing storage temperature. A focus should be placed on the results of intermediate study to establish the shelf life of the drug product stored at room temperature. Although the submitted data include only the results of the 12-month intermediate study using 1 batch, there is no choice but to establish the shelf-life based on the above study data because the drug product is

intended for use in patients with the rare and serious disease. It is acceptable to select the shelf-life of 20 months for the drug product stored at room temperature, based on the results of the intermediate study and on the results of the regression analysis performed based on the data of said study.

The additional intermediate study using 3 commercial-scale batches of the drug product should be conducted immediately, and the shelf-life of the drug product should be validated based on the results of the study as soon as they become available.

2.R.2 Photostability of drug product

The data of the photostability testing of the drug product had not been submitted at the filing of the application. PMDA asked the applicant to conduct a photostability testing in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline entitled "Stability Testing: Photostability Testing of New Drug Substances and Products" (ICH Q1B Guideline). A photostability testing is currently being conducted by the applicant.

The conclusion of PMDA, based on results from the ongoing photostability testing, is presented in the Review Report (2).

2.R.3 Analytical procedures for drug substance

Validation characteristics other than specificity were not evaluated in the validation of the analytical procedure for acetic acid, a related substance included in the purity test of the drug substance. PMDA asked the applicant to evaluate validation characteristics other than specificity in accordance with the ICH guideline entitled "Validation of Analytical Procedures: Methodology" (ICH Q2B Guideline). The validation of the analytical procedure for acetic acid, a related substance specified for the purity test, is currently being conducted by the applicant.

The conclusion of PMDA, based on results from the ongoing validation of the analytical procedure, is presented in the Review Report (2).

2.R.4 Novel excipient

The drug product contains hypromellose, a novel excipient, in an amount greater than that contained in existing drug products in oral dosage forms.

PMDA concluded that hypromellose contained in the drug product is compliant with the Japanese Pharmacopoeia and that there are no problems with the specifications or stability. From the document submitted, PMDA also concluded that there are no safety problems with the amount of hypromellose contained in the drug product proposed in the present application.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted the results of primary pharmacodynamic studies and safety pharmacology studies as the nonclinical pharmacological data of aceneuramic acid. Results from main studies are described in sections below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effect to increase sialic acid content in cells derived from patients with DMRV (Reference CTD 4.2.1.1-1, *J Biol Chem.* 2004;279:11402-7)

Dermal fibroblasts and myotubular cells[2)] derived from patients with DMRV and healthy individuals were cultivated in the serum-free medium for 24 hours, after which sialic acid levels in the cells were measured. Sialic acid levels in cells derived from patients with DMRV were 60% to 74% lower than those in cells derived from healthy individuals. When cells derived from patients with DMRV were cultivated in the serum-free medium supplemented with aceneuramic acid (a type of sialic acid) at 5 mmol/L or with N-acetylmannosamine (ManNAc) at 5 mmol/L, or in the medium supplemented with 10% fetal calf serum, sialic acid levels in the cells were comparable to those in healthy individual-derived cells.

3.1.2 *In vivo* studies

3.1.2.1 Effect on DMRV model mice (Reference CTD 4.2.1.1-2, *Nat Med.* 2009;15:690-5)

The effect of aceneuramic acid and ManNAc was investigated in the mouse model of DMRV (*Gne*$^{-/-}$h*GNED*176V-Tg), which was genetically engineered to express only mutant human *GNE* gene (p.D207V) in murine *GNE* gene-deleted mice (*Hum Mol Genet*. 2007;16:2669-82). DMRV mice 10 to 20 weeks of age were allowed to drink water (control) or water containing aceneuramic acid or ManNAc (both substances were adjusted to 20 mg/kg/day) ad libitum up to Week 54 to 57 after birth. The unaffected litter mates[3)] of DMRV mice were also allowed to drink water or water containing aceneuramic acid or ManNAc. DMRV mice in the aceneuramic acid group and the ManNAc group showed a higher survival rate and higher body weight than those in the control group. The following parameters were lower in DMRV mice than in their litter mates: Serum sialic acid concentration, sialic acid levels in muscular tissues, treadmill walking distance, weight and cross-sectional area of gastrocnemius muscle and tibialis anterior muscle, and isometric contractility and tonic contractility of gastrocnemius muscle. In contrast, these parameters were higher in DMRV mice in the aceneuramic acid group and the ManNAc group than in DMRV mice in the control group. Serum creatinine kinase activity level and the number of rimmed vacuoles and amyloid deposits in gastrocnemius muscles were higher in DMRV mice than in their litter mates, whereas the levels were lower in DMRV mice in the aceneuramic acid group and the ManNAc group than in DMRV mice in the control group.

3.2 Safety pharmacology

Table 4 shows the outline of the results of the safety pharmacology studies.

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2) Dermal fibroblasts (4 samples in total) were collected from the following patients: One patient with compound heterozygous mutations in the *GNE* gene (p.D207V and p.I503T) and 1 patient with homozygous mutation in *GNE* gene (p.D207V). Myotubular cells (4 samples) were collected from a patient with *GNE* gene without exon 4.

3) Mice with *Gne*$^{+/-}$ or *Gne*$^{+/-}$h*GNED*176V-Tg genotype that show no phenotype (*Hum Mol Genet.* 2007;16:2669-82).

Table 4. Outline of results of safety pharmacology studies

Organ system	Test system	Evaluation parameters and methods	Dose or concentration	Route of administration	Findings	CTD
Central nervous system	Rats (6 males/group)	Modified Irwin method	0,[a] 20, 200, 2000 mg/kg	p.o.	No effect	4.2.1.3-1
Cardiovascular system	HEK293 cells (5 samples)	hERG current	0,[a] 0.6, 2, 6, 20 mmol/L	*in vitro*	No effect [b]	4.2.1.3-3
	Dogs (4 males)	Blood pressure (systolic, diastolic, mean), heart rate, electrocardiogram (PQ, QRS, QT, QTcF intervals)	0,[a] 20, 200, 2000 mg/kg[c]	p.o.	No effect	4.2.1.3-2
Respiratory system	Dogs (4 males)	Respiratory rate, tidal volume, minute ventilation	0,[a] 20, 200, 2000 mg/kg[c]	p.o.	No effect	4.2.1.3-2

a) Vehicle: Water for injection (pH adjusted to approximately 3 with hydrochloric acid)
b) At 20 mmol/L, the current exceeded 100 pA within 10 minutes after addition of aceneuramic acid, precluding evaluation in the 2 samples studied.
c) Four-treatment, 4-period crossover design (interval ≥6 days)

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about the efficacy of aceneuramic acid in patients with DMRV, based on the pathogenesis of DMRV:

DMRV is a disease that causes a gradual decline in muscle strength associated with the atrophy of muscle tissue and degeneration of muscle fibers, mainly in distal muscles. Although the pathogenesis of DMRV has not been elucidated, mutations in the *GNE* gene encoding the GNE/MNK enzyme involved in the biosynthesis of sialic acids such as aceneuramic acid, are thought to be the cause of the disease (*Nat Genet.* 2001;29:83-7). Patients with DMRV have the following abnormalities: (1) Lower sialic acid levels in muscle tissues due to a decrease in GNE/MNK activity caused by mutations in the GNE gene (*J Biol Chem.* 2004;279:11402-7); and (2) reduced sialylation of glycoproteins (α-dystroglycan, neural cell adhesion molecule, neprilysin, etc.) in muscle tissues (*Mol Genet Metab.* 2004;81:196-202, *Neurology.* 2006;66:755-8, *J Neurochem.* 2008;105:971-81).In addition, reduced sialylation is associated with oxidative stress, which leads to muscle atrophy and weakness in patients with DMRV (*Hum Mol Genet.* 2017;26:3081-93). These findings suggest that mutations in the *GNE* gene result in a decrease in GNE/MNK activity, leading to reduced sialic acid biosynthesis in muscle tissue, and then to reduced sialylation of glycoproteins which contributes to muscle tissue atrophy and fibrosis in patients with DMRV.

Aceneuramic acid is one of sialic acids that are biosynthesized at reduced levels in the muscle tissues of patients with DMRV due to mutations in the *GNE* gene. The oral administration of aceneuramic acid to the DMRV mouse model led to an increase in sialic acid levels in muscle tissues, resulting in suppression of the progression of muscle tissue atrophy and fibrosis, and muscle weakness [see Section 3.1.2.1]. The applicant considers that the administration of aceneuramic acid to patients with DMRV can normalize hyposialylation in muscle tissues, thereby suppressing muscle tissue atrophy and fibrosis, and potentially leading to suppression of muscle weakness progression.

Based on the submitted study data and the applicant's explanation, PMDA considers that aceneuramic acid is expected to suppress the progression of muscle weakness in patients with DMRV.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted the data of the following non-clinical pharmacokinetic studies on aceneuramic acid: Studies on absorption, distribution, metabolism, and excretion in rats, dogs, and rabbits. Aceneuramic acid concentration in biomaterials was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation (LLOQ) = 10 or 25 μg/mL). In studies conducted using ^{14}C-labeled aceneuramic acid, the radioactivity concentration in biomaterials was measured using a liquid scintillation counter (LLOQ = twice the level in the blank sample). The key study data obtained are presented in the subsections below.

4.1 Absorption

4.1.1 Single-dose administration

Table 5 shows the pharmacokinetic parameters of total serum radioactivity following a single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg to male rats (CTD 4.2.2.2-1).

Table 5. Pharmacokinetic parameters of total serum radioactivity following single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg

N	$C_{0\ h}$ a) (μg eq./mL)	$AUC_{0\text{-last}}$ (μg eq.•h/mL)	CL (mL/h/kg)	Vd (mL/kg)	$t_{1/2\alpha}$ (h) b)	$t_{1/2\beta}$ (h) c)
3	111 ± 14	81.84 ± 18.76	197 ± 55	2773 ± 513	0.4 ± 0.2	19.1 ± 3.7

Mean ± standard deviation (SD)
a) Initial radioactivity concentration calculated by non-compartment analysis
b) Calculated using serum total radioactivity concentrations at 2 to 60 minutes post-dose.
c) Calculated using serum total radioactivity concentrations at 3 to 24 hours post-dose.

Table 6 shows change over time in total serum aceneuramic acid (including free aceneuramic acid in serum and aceneuramic acid bound to carbohydrate chains within the body [including the intrinsic aceneuramic acid]) following a single oral administration of aceneuramic acid to male rats and male dogs (Reference CTD 4.2.2.2-5 and 4.2.2.2-6). Administration of aceneuramic acid resulted in an increase in serum total aceneuramic acid levels only in dogs receiving aceneuramic acid 2000 mg/kg.

Table 6. Change over time in total serum aceneuramic acid following single oral administration of aceneuramic acid

Animal species	Dose (mg/kg)	N	Sampling point						
			Before administration	10 minutes post-dose	20 minutes post-dose	30 minutes post-dose	1 hour post-dose	2 hours post-dose	4 hours post-dose
Rats	200	5 a)	563 ± 37	539 ± 43	539 ± 42	508 ± 24	531 ± 23	529 ± 39	506 ± 26
	2000	5 a)	554 ± 34	553 ± 46	523 ± 39	545 ± 15	539 ± 49	511 ± 44	531 ± 13
Dogs	200	4	530 ± 19	514 ± 15	511 ± 14	508 ± 6	504 ± 18	504 ± 11	515 ± 22
	2000	4	557 ± 25	590 ± 52	609 ± 46	636 ± 53	606 ± 46	562 ± 9	556 ± 20

Unit, μg/mL; mean ± SD
a) 15 animals measured before administration of aceneuramic acid

4.1.2 Repeated-dose studies

Toxicokinetics was investigated in a repeated oral dose toxicity study in rats and dogs. Table 7 shows the pharmacokinetic parameters of total serum aceneuramic acid (including free aceneuramic acid in serum and aceneuramic acid bound to carbohydrate chains within the body [including the intrinsic aceneuramic acid]) following repeated once-daily oral administration of aceneuramic acid in each study (CTD 4.2.3.2-2 and 4.2.3.2-3).

Table 7. Pharmacokinetic parameters of total serum aceneuramic acid following once-daily repeated oral administration of aceneuramic acid

Animal species	Sampling point	Dose (mg/kg)	Sex (No. of animals)	Pre-dosing concentration (μg/mL)	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24\ h}$ (μg•h/mL)	CTD
Rats	Day 1	200	Male (5)	-	565 ± 44	0.50 [0.50, 24]	12900 ± 779	4.2.3.2-2
			Female (5)	-	611 ± 31	1.0 [0.50, 24]	13600 ± 750	
		600	Male (5)	-	588 ± 40	24 [0.50, 24]	13200 ± 1424	
			Female (5)	-	586 ± 25	0.50 [0.50, 24]	12700 ± 683	
		2000	Male (5)	-	572 ± 60	0.50 [0.50, 24]	12400 ± 1205	
			Female (5)	-	565 ± 24	1.0 [0.50, 24]	12200 ± 492	
	Day 182	200	Male (5)	823 ± 61	849 ±47	1.0 [0, 24]	18800 ± 976	
			Female (5)	735 ± 81	740 ± 77	0 [0, 24]	16300 ± 1597	
		600	Male (5)	725 ± 62	779 ± 74	24 [0, 24]	17000 ± 1756	
			Female (5)	640 ± 61	646 ± 59	0 [0, 0.50]	13900 ± 1274	
		2000	Male (5)	790 ± 78	836 ± 74	1.0 [0.50, 24]	18200 ± 1401	
			Female (5)	671 ± 44	691 ± 43	0.50 [0.50, 1.0]	15000 ± 921	
Dogs	Day 1	200	Male (4)	494 ± 17	525 ± 11	8.0 [8.0, 8.0]	12200 ± 275	4.2.3.2-3
			Female (4)	485 ± 72	496 ± 62	6.0 [0, 24]	11600 ± 1406	
		600	Male (4)	509 ± 16	517 ± 18	1.5 [1.0, 8.0]	12000 ± 265	
			Female (4)	497 ± 22	521 ± 12	1.1 [0.17, 8.0]	12200 ± 191	
		2000	Male (6)	483 ± 38	569 ± 61	1.0 [1.0, 2.0]	11800 ± 870	
			Female (6)	497 ± 53	591 ± 89	1.0 [0.50, 1.0]	12000 ± 1303	
	Day 91	200	Male (4)	543 ± 26	562 ± 17	5.0 [0, 8.0]	13100 ± 289	
			Female (4)	511 ± 35	520 ± 32	0.25 [0, 8.0]	12100 ± 806	
		600	Male (4)	542 ± 46	578 ± 44	0.50 [0.17, 4.0]	13200 ± 1103	
			Female (4)	459 ± 15	500 ± 20	0.34 [0.17, 4.0]	11400 ± 520	
		2000	Male (6)	526 ± 59	608 ± 75	1.0 [0.50, 1.0]	12700 ± 1661	
			Female (6)	511 ± 59	623 ± 101	1.0 [0.50, 1.0]	12500 ± 1618	
	Day 273	200	Male (4)	462 ± 6	490 ± 20	8.0 [8.0, 8.0]	11400 ± 316	
			Female (4)	463 ± 45	474 ± 37	6.0 [0, 8.0]	10800 ± 886	
		600	Male (4)	459 ± 56	477 ± 61	1.3 [0.17, 8.0]	11000 ± 1476	
			Female (4)	456 ± 51	493 ± 39	4.3 [0, 8.0]	11300 ± 748	
		2000	Male (6)	479 ± 36	584 ± 49	1.0 [0.50, 1.0]	12000 ± 662	
			Female (6)	478 ± 41	677 ± 160	1.0 [0.50, 1.0]	12100 ± 1046	

Mean ± SD; -, Not measured
a) Median [range]

4.2 Distribution

4.2.1 Tissue distribution

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg to 3 male rats, tissue distribution[4)] of the radioactivity was investigated up to 24 hours post-dose. The radioactivity concentrations peaked at 0.5 hours post-dose in tissues other than the brain, pituitary gland, small intestine, thymus, and liver, and decreased at 3 hours post-dose in tissues other than the small intestine and brain. The radioactivity was still detectable at 24 hours post-dose in all tissues. Tissues exhibiting higher radioactivity concentrations than serum included the kidneys and bladder at 0.5 hours post-dose, and the bladder, kidneys, small intestine, spleen, blood, liver, and stomach at 3 hours post-dose (CTD 4.2.2.2-1).

4.2.2 Protein binding

When ^{14}C-labeled aceneuramic acid 18 μg/mL was added to rat plasma, plasma protein binding (determined by ultrafiltration) was 1.2% (Reference CTD 4.2.2.2-2: *Xenobiotic Metabolism and Disposition.* 1991;6:209-17).

4) The radioactivity concentrations were investigated in the following tissues: Blood, serum, brain, pituitary gland, eyeball, submandibular gland, thyroid gland, trachea, thymus, heart, lungs, liver, adrenal glands, kidneys, spleen, pancreas, testes, skin, bone marrow, white adipose tissue, bladder, stomach, small intestine, large intestine (including cecum), sternocleidomastoid muscle, palmar interosseous muscle, tibialis anterior muscle, biceps femoris muscle, quadriceps femoris muscle, and gastrocnemius muscle.

4.2.3 Distribution in blood cells

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg to rats, the distribution rate[5)] in blood cells, calculated by radioactivity concentration in blood and serum at 30 minutes post-dose, was 11.0% (CTD 4.2.2.2-1).

4.2.4 Placental transfer

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 80 μg/kg to 3 rats on Gestation Day 19, radioactivity became detectable in fetal tissues (brain, lungs, liver, and intestinal tract) within 24 hours post-dose, suggesting that aceneuramic acid passes through the placenta into fetuses (Reference CTD 4.2.2.3-1: *Xenobiotic Metabolism and Disposition.* 1991;6:219-25).

4.3 Metabolism

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg to rats, metabolites in serum and urine were investigated. At 3 hours post-dose, 2 metabolites (both with unidentified structures, accounting for 45.3% and 7.8% of the serum radioactivity) were detected in the serum, in addition to unchanged aceneuramic acid (accounting for 25.5% of the serum radioactivity). In urine collected from 1 to 24 hours post-dose, unchanged aceneuramic acid was predominantly detected (94.9% of urinary radioactivity), along with the metabolite ManNAc (1.7%) (CTD 4.2.2.2-1).

When ^{14}C-labeled aceneuramic acid (60 μg) was incubated *in vitro* with rat intestinal content for 6 hours, 21.7% of the added radioactivity was recovered as carbon dioxide, suggesting that aceneuramic acid is metabolized to carbon dioxide in the rat gastrointestinal tract (Reference CTD 4.2.2.2-3: *Xenobiotic Metabolism and Disposition.* 1991;6:237-42].

Aceneuramic acid is metabolized to ManNAc and pyruvate by N-acetylneuraminic acid lyase in the cytoplasm, and after conversion to CMP-N-acetylneuraminic acid within the cell nucleus, it is transferred to the Golgi apparatus and then incorporated into glycans (*J Biol Chem.* 1960;235:2529-37, *Carbohydr Res.* 2022;516:108561). In non-human mammals, aceneuramic acid is hydroxylated at its acetyl group and metabolized into N-glycolylneuraminic acid (*J Biol Chem.* 1998;273:15866-71).

4.4 Excretion

4.4.1 Excretion into urine, feces, expired air, and bile

Following a single oral administration of ^{14}C-labeled aceneuramic acid 80 μg/kg to male rats (n = 3), 6.1%, 29.5%, and 62.4% of the total administered radioactivity were excreted in urine, feces, and expired air, respectively, within 72 hours post-dose [(Reference CTD 4.2.2.2-3, *Xenobiotic Metabolism and Disposition.* 1991;6:237-42].

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 20 mg/kg to male rats (n = 3), 92.4% and 0.67% of the total administered radioactivity were excreted in urine (including that in cage washings) and feces, respectively, within 24 hours post-dose (CTD 4.2.2.2-1).

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5) Distribution in blood cells was calculated using the commonly used normal hematocrit value of 0.45.

Following intratracheal administration of ^{14}C-labeled aceneuramic acid 80 μg/kg to male rats (n = 5), the biliary excretion of the total administered radioactivity within 6 hours post-dose was investigated. No radioactivity was detected in the bile. The urinary excretion of the total administered radioactivity within 6 hours post-dose was 98.6% (Reference CTD 4.2.2.2-2, *Xenobiotic Metabolism and Disposition.* 1991;6:209-17).

4.4.2 Excretion in milk

Following a single intravenous administration of ^{14}C-labeled aceneuramic acid 80 μg/kg to female rats (n = 5) from Postpartum Days 10 to 12, the radioactivity was detected in milk within 3 hours post-dose, suggesting that aceneuramic acid is excreted in milk (Reference CTD 4.2.2.3-1, *Xenobiotic Metabolism and Disposition.* 1991;6:219-25).

4.R Outline of the review conducted by PMDA

4.R.1 Non-clinical pharmacokinetics of aceneuramic acid

The applicant's explanation about the non-clinical pharmacokinetics of orally administered aceneuramic acid:

After oral administration, aceneuramic acid is partially metabolized by enteric bacteria within the digestive tract, and unchanged aceneuramic acid and metabolites are absorbed by the digestive tract. The oral absorption rate of aceneuramic acid is estimated to be approximately 6%, in view of (1) the urinary excretion of the total radioactivity after oral administration of radiolabeled aceneuramic acid in rats; and (2) the fact that most of intravenously administered aceneuramic acid in rats was excreted as unchanged aceneuramic acid in urine [see Sections 4.3 and 4.4.1]. Most of the absorbed aceneuramic acid is excreted unchanged in the urine, whereas a portion of aceneuramic acid is distributed to tissues, where it is incorporated into glycolipids and glycoproteins and utilized in the body, or it is metabolized by intracellular enzymes into ManNAc, pyruvate, N-glycolylneuraminic acid, etc. [see Section 4.3].

Based on the submitted data and other relevant materials, PMDA considers that the pharmacokinetics of aceneuramic acid following oral administration can be understood to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and safety evaluation of impurities in the drug substance and the drug product.

5.1 Single-dose toxicity

A single oral dose toxicity study of aceneuramic acid was conducted in rats (Table 8). No acute toxicity was observed, nor were there any death attributable to administration of aceneuramic acid. The approximate lethal dose of oral aceneuramic acid was >4000 mg/kg.

Table 8. Summary of the results of the single-dose administration study

Test system	Route of administration	Dose (mg/kg)	Main finding	Approximate lethal dose (mg/kg)	CTD
Male and female rats (Wistar)	p.o.	0,[a)] 4000	Transient diarrhea	>4000	Reference 4.2.3.1-1

a) Vehicle, Water for injection

5.2 Repeated-dose toxicity

A 26-week repeated oral dose toxicity study in rats and a 39-week repeated oral dose toxicity study in dogs were conducted (Table 9). No signs of toxicity related to administration of aceneuramic acid were observed in rats or dogs.

Table 9. Summary of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	CTD
Male and female rats (SD)	p.o.	26 weeks (once daily) + 4 weeks of recovery	0,[a)] 200, 600, 2000	2000: Loose stool,[b)] increased urinary sodium concentration[c)] Reversible	2000	4.2.3.2-2
Male and female dogs (beagle)	p.o.	39 weeks (once daily) + 4 weeks of recovery[d)]	0,[a)] 200, 600, 2000	≥200: Loose stool/watery diarrhea/ mucous feces[b)] ≥600: Corneal opacity[e)] 2000: Increased urinary sodium concentration[c)] and coronary arteritis[f)] Reversible (except corneal opacity)	2000	4.2.3.2-3

a) Water for injection (pH adjusted to approximately 3 with hydrochloric acid). In the aceneuramic acid groups, aceneuramic acid solution of each concentration was prepared using water for injection (pH adjusted to approximately 3 with sodium hydroxide solution).
b) The applicant determined that these findings had little toxicological significance because they were not accompanied by any histopathological change or clinical signs.
c) The finding was caused by sodium hydroxide used for adjusting the pH of the dosing solution and no effect was observed on blood sodium concentration, based on which the applicant considered that the increased urinary sodium had little toxicological significance.
d) Only the 2000 mg/kg group underwent the recovery period.
e) Localized opaque spots were observed. Although the incidence of the event was higher than the laboratory historical value, the applicant considered that the findings were spontaneous events, judging from the degree of the finding, among others.
f) The finding was not accompanied by changes in cardiac muscles and consistent with the finding of coronary arteritis (*Toxicol Pathol*. 2003;31:25-31), based on which the applicant considered that the finding was not causally related to aceneuramic acid.

5.3 Genotoxicity

Genotoxicity studies on aceneuramic acid included a bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral lymphocytes (*in vitro* studies) and micronucleus assay in mouse bone marrow (*in vivo* study) (Table 10). Based on the negative results in all assays, the applicant considered that aceneuramic acid is not genotoxic.

Table 10. Summary of the results of genotoxicity studies

Study type		Test system	Metabolic activation (duration)	Concentration or dose	Results	CTD
in vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, and TA1537 *Escherichia coli*: WP2*uvrA*	S9-/+	0,[a] 50, 158, 500, 1581, 5000 (μg/plate)	Negative	4.2.3.3.1-1
	Chromosomal aberration assay in cultured mammalian cells	Human peripheral lymphocytes	S9+ (4 hours)	0,[a] 80, 160, 310 (μg/mL)	Negative	4.2.3.3.1-2
			S9- (4 and 21 hours)	0,[a] 80, 160, 310 (μg/mL)		
in vivo	Micronucleus assay in rodents	Male and female mice (CD-1) Bone marrow		0,[a] 500, 1000, 2000 (mg/kg) (p.o. twice)	Negative	4.2.3.3.2-1

a) Vehicle, water for injection

5.4 Carcinogenicity

No carcinogenicity study was conducted on aceneuramic acid.

The applicant's explanation:

Based on the following points, the risk of carcinogenesis associated with clinical use of this agent is low.

- Aceneuramic acid is a component present *in vivo* and is a type of sialic acid located at the terminal end of glycans on the cell surface.
- No clear association with carcinogenesis has been reported either in sialuria characterized by excessive sialic acid concentrations in the cytoplasm or in free sialic acid storage disorders, a neurodegenerative disorder caused by increased accumulation of free sialic acid in lysosomes. (https://www.ncbi.nlm.nih.gov/books/NBK1470/ [last accessed on January 25, 2024]).
- Aceneuramic acid is not genotoxic [see Section 5.3]. There were no findings suggestive of carcinogenesis in the repeated-dose toxicity studies of aceneuramic acid [see Section 5.2].

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function in rats were conducted (Table 11). Aceneuramic acid had no effect on parental animals, embryos/fetuses, or neonates in any of the studies.

Table 11. Summary of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Duration of treatment	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	CTD
Studies of fertility and early embryonic development to implantation	Male rats (SD)	p.o.	From 2 weeks prior to mating until 42 days after mating (once daily)	0,[a] 200, 600, 2000	Parental animals: 2000: Loose stool	Parental animals (male fertility): 2000	4.2.3.5.1-1
	Female rats (SD)		From 2 weeks prior to mating until Gestation Day 7 (once daily)		Parental animals: 2000: Loose stool Fertility and early embryonic development: No finding	Parental animals (female fertility): 2000 Fertility and early embryonic development: 2000	
Embryo-fetal development studies	Female rats (SD)	p.o.	Gestation Day 6 to 17 (once daily)	0,[a] 200, 600, 2000	Maternal animals: No finding Embryos/fetuses: No finding	Maternal animals: 2000 Embryo-fetal development: 2000	4.2.3.5.2-1
	Pregnant rabbits (NZW)	p.o.	Gestation Day 6 to 18 (once daily)	0,[a] 600, 2000	Maternal animals: No finding Embryos/fetuses: No finding	Maternal animals: 2000 Embryo-fetal development: 2000	4.2.3.5.2-2 4.2.3.5.2-3
Study of effects on pre- and postnatal development, including maternal function	Pregnant rats (SD)	p.o.	Gestation Day 6 to Postpartum Day 20 (once daily)	0,[a] 200, 600, 2000	Maternal animals: No finding F_1 offspring: No finding	Maternal animals (general toxicity): 2000 F_1 offspring: 2000	4.2.3.5.3-1

a) Water for injection (pH adjusted to approximately 3 with hydrochloric acid). In the aceneuramic acid groups, aceneuramic acid solution of each concentration was prepared using water for injection (pH adjusted to approximately 3 with sodium hydroxide solution).

5.6 Safety assessment of impurities

The drug substance and the drug product contain 9 impurities that are present in a level greater than the qualification threshold as per the guidelines entitled “Partial revision of ‘Revision of the Guidelines on Impurities in New Drug Substances’” (ICH Q3A Guideline) and “Revision of ‘Revision of the Guidelines on Impurities in New Drug Products’” (ICH Q3B Guideline). The applicant evaluated the general toxicity and genotoxicity of these impurities and submitted the following results:

- General toxicity: The no-observed-adverse-effect level (NOAEL) determined in the 39-week repeated oral toxicity dose study in dogs was 2000 mg/kg. This dose contained impurities at levels greater than the daily intake of each impurity calculated from the upper specification limit for the drug substance and drug product at the clinical dose (6 g/day) of aceneuramic acid, and there were no safety concerns about the clinical dose of aceneuramic acid [see Section 5.2].
- Genotoxicity (induction of gene mutation): The test substance (drug substance) containing the impurities in a certain level (albeit below the upper specification limit for 8 of the 9 identified impurities [except Impurity A]) had a negative result in the bacterial reverse mutation assay [see Section 5.3]. Of the 8 impurities, 6 impurities other than Impurities B and C had a negative result in the assessment of mutagenicity based on the (Quantitative) Structure-Activity Relationship ([Q]SAR). The mutagenicity of Impurity A has not been evaluated, even with the (Q)SAR analysis.
- Genotoxicity (chromosome aberration induction): The maximum dose of aceneuramic acid (2000 mg/kg) used in the micronucleus assay in rodents contained 8 impurities (of the 9 identified impurities [except Impurity A]) at levels greater than the exposure levels calculated from the upper

specification limit for the drug substance and drug product at the clinical dose (6 g/day) of aceneuramic acid. The assay produced a negative result [see Section 5.3]. Chromosome aberration-inducing activity of Impurity A has not been evaluated.

5.R Outline of the review conducted by PMDA

5.R.1 Genotoxicity of Impurities A, B, and C

PMDA requested the applicant to conduct genotoxicity studies on 1 impurity (Impurity A) contained in the drug substance and the drug product and 2 impurities (Impurity B and Impurity C) contained in the drug substance, taking account of the following:

- Since Impurity A was not contained in the test substance used in the genotoxicity study (Table 10), it has not been evaluated for its mutagenicity or potential to induce chromosomal aberrations.
- The levels of Impurities B and C contained in the test substances used in the bacterial reverse mutation assay of aceneuramic acid (CTD 4.2.3.3.1-1) were below the specification limit [see Section 5.6].
- The applicant determined that the chemical structures of Impurities A, B, and C could not be elucidated, and thus, the assessment of mutagenicity based on the (Q)SAR was impossible.

The applicant's explanation:
The applicant initiated additional genotoxicity studies (the bacterial reverse mutation assay and the chromosomal aberration assay). However, it will take some time to complete these additional genotoxicity studies and obtain the results, including time for the preparation of test substances containing adequate amounts of Impurities A, B, and C.

PMDA's view:
Impurities A, B, and C are present at levels greater than the qualification threshold according to the ICH Q3A and Q3B guidelines. For the regulatory submission for aceneuramic acid, the toxicity (including genotoxicity) of the impurities should be clarified based on appropriate studies. However, aceneuramic acid is indicated for DMRV, a rare and serious disease with no available treatments worldwide and therefore with a high medical need for its treatment [see Section 7.R.2]. Even if the genotoxicity of these impurities is currently unknown, it is feasible to make aceneuramic acid available for use in clinical settings in Japan, as long as the applicant advises that physicians and patients should fully understand that aceneuramic acid contains impurities for which the possibility of genotoxicity cannot be ruled out, before making informed decisions on its use.

The bacterial reverse mutation assays using Impurities A, B, and C, and the chromosomal aberration assay using Impurity A, should be promptly completed. Upon obtaining the test results, the applicant should immediately provide the information to healthcare professionals and take necessary measures.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Biopharmaceutic studies and associated analytical methods

The total aceneuramic acid concentration in serum was measured by LC-MS/MS (LLOQ = 1, 10, or 50 μg/mL), and free aceneuramic acid concentration in serum was measured by LC-MS/MS (LLOQ =

0.020 or 0.0400 μg/mL). The total aceneuramic acid concentration in urine was measured by LC-MS/MS (lower limit of quantification, 1 or 5.00 μg/mL), and free aceneuramic acid concentration in urine was measured by LC-MS/MS (LLOQ = 1.00 μg/mL).

The formulations of aceneuramic acid used in clinical studies include immediate-release tablets (100 mg) and extended-release tablets (325 mg and 500 mg). The Japanese phase I study (1) (Sialic Acid-1 study) used the 100 mg immediate-release tablets, while the foreign phase I study (Study UX001-CL101 [CTD 5.3.3.2-3] ["Study CL101"]) used the 325 mg and 500 mg extended-release tablets. Further, the 500 mg extended-release tablets were used in subsequent major clinical studies of aceneuramic acid (Japanese phase I study (2) [Sialic Acid-2 study], Japanese phase III study (1) [Sialic Acid-3 study], Japanese phase III study (2) [Study NPC-09-1], Japanese long-term treatment study [Sialic Acid-4 study], foreign phase II study [Study UX001-CL201 (Reference CTD 5.3.5.1-3) ("Study CL201")], and foreign phase III study [Study UX001-CL301 (Reference CTD 5.3.5.1-4) ("Study CL301")]). The to-be-marketed formulation in Japan is the 500 mg extended-release tablet, which differs from the 500 mg extended-release tablet used in the main clinical studies only in terms of the presence of film coating, with both formulations demonstrating their equivalence in dissolution testing.

The key study results are described in the subsections below.

6.1.1 Food effect (CTD 5.3.3.2-3, Study CL101)

The effect of food on the pharmacokinetics of aceneuramic acid was evaluated in the single-dose part of the study in non-Japanese patients with DMRV [see Section 6.2.2.2 for the outline of the study]. Table 12 shows the pharmacokinetic parameters of free aceneuramic acid in serum, corrected for pre-dose concentration, following a single oral administration of aceneuramic acid under fasting conditions or within 30 minutes after the intake of a high-fat, high-caloric meal. In the 6000 mg group receiving the 500 mg extended-release tablets, no significant change in C_{max} was observed regardless of fasting or postprandial conditions, whereas $AUC_{0\text{-}24}$ increased approximately 1.5-fold and t_{max} delay was delayed when aceneuramic acid was given under postprandial conditions.

Table 12. Pharmacokinetic parameters of free aceneuramic acid in serum, corrected for pre-dose concentration, following single administration of aceneuramic acid in non-Japanese patients with DMRV

Dose	Dietary condition	No. of subjects evaluated	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24}$ (μg•h/mL)	$t_{1/2}$ (h)
650 mg	Fasting	6	0.129 (62.9)	6.0 [1.0, 20]	0.914 (45.5)	8.40[a)]
	Postprandial	6	0.054 (32.6)	8.0 [4.0, 16]	0.415 (70.3)	4.03[a)]
1950 mg	Fasting	6	0.163 (51.3)	4.0 [2.0, 8.0]	1.22 (56.4)	2.86, 3.55[b)]
	Postprandial	6	0.171 (55.1)	8.0 [4.0, 8.1]	1.64 (33.0)	1.64[a)]
2925 mg	Fasting	6	0.364 (64.5)	3.0 [1.0, 4.2]	2.22 (55.7)	1.15, 3.34[b)]
	Postprandial	6	0.293 (19.7)	4.0 [4.0, 4.1]	2.58 (31.0)	3.36, 3.73[b)]
4875 mg	Fasting	4	0.760 (46.2)	3.0 [1.1, 4.2]	4.72 (34.8)	2.75 ± 0.743
	Postprandial	4	0.472 (44.8)	6.0 [4.0, 8.0]	4.02 (35.2)	3.18 ± 0.517[c)]
6000 mg	Fasting	6	0.351 (37.6)	3.0 [2.0, 8.0]	2.59 (49.2)	2.46 ± 1.06[d)]
	Postprandial	6	0.324 (34.3)	10 [4.0, 12]	3.93 (20.8)	3.71 ± 1.07

$t_{1/2}$, Mean ± SD; C_{max} and $AUC_{0\text{-}24}$, Geometric means (coefficient of variation [CV], %); t_{max}, Median [range]
The pharmacokinetic parameters were calculated using the values at each sampling point, subtracting the values at the same time point on the day before the administration of aceneuramic acid (if the values at the same time point were not available, the average of all values on the day before the first dose of aceneuramic acid was used). If the corrected values were negative, they were treated as zero.
a) N = 1 (individual value), b) N = 2 (individual values), c) N = 3, d) N = 4

6.2 Clinical pharmacology

6.2.1 Studies using human biomaterials

(a) Plasma protein binding (Reference CTD 4.2.2.2-2, *Xenobiotic Metabolism and Disposition.* 1991:6;209-17)

After the addition of ^{14}C-labeled aceneuramic acid (18 μg/mL) to human plasma 1 mL, the plasma protein binding rate (determined by ultrafiltration) was 3.1%.

(b) Study of metabolites in humans

Metabolites of aceneuramic acid in human samples were not investigated.

In humans, aceneuramic acid is metabolized to ManNAc and pyruvate by N-acetylneuraminic acid lyase in the cytoplasm, and after conversion to CMP-N-acetylneuraminic acid within the cell nucleus, it is transferred to the Golgi apparatus and then incorporated into glycans (*Carbohydr Res.* 2022;516:108561).

(c) Enzyme inhibition and enzyme induction

The inhibitory effect of aceneuramic acid on P450 isoforms in human liver microsomes (0.015-15 mmol/L against CYP3A and 0.16-160 μmol/L against isoforms other than CYP3A) was investigated using substrates[6] of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Aceneuramic acid inhibited the metabolism of the substrates of CYP3A (testosterone and midazolam) with the inhibition rate of 51% and 34%, respectively, at 15 mmol/L, but did not show a clear inhibitory effect on other isoforms within the concentration range investigated (Reference CTD 4.2.2.6-1).

The inducing effect of aceneuramic acid (1.5-8800 μmol/L) on CYP1A2, CYP2B6, and CYP3A4 in cryopreserved human hepatocytes was investigated based on messenger ribonucleic acid (mRNA) expression levels. CYP1A2 mRNA levels were not increased by aceneuramic acid within the range of concentrations investigated. In contrast, the expression of CYP2B6 mRNA increased by 2.20-fold in the presence of aceneuramic acid at 8800 μmol/L in one of 3 batches of hepatocytes (18.1% increase over mRNA levels in hepatocytes treated with the positive control [phenobarbital 750 μmol/L][7]). The expression of CYP3A4 mRNA increased by 2.10- and 2.71-fold in the presence of aceneuramic acid at 1000 and 8800 μmol/L, respectively, in one of 3 batches of hepatocytes (1.15% and 1.79% increases, respectively,[7] over mRNA levels in hepatocytes treated with the positive control [rifampicin 20 μmol/L]) (Reference CTD 4.2.2.6-2).

According to the applicant's explanation, aceneuramic acid is unlikely to cause drug-drug interactions mediated by the inhibition or induction of P450 isoforms, in view of the above results and the following clinical findings: (1) In the Japanese phase I study (Sialic Acid-2 study), the maximum serum free aceneuramic acid concentration in individual subjects was approximately 1.6 μg/mL (5.2 μmol/L) after a single dose of aceneuramic acid 2 g (the clinical dose); and (2) the maximum

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[6] CYP1A2, Phenacetin; CYP2B6, Efavirenz; CYP2C8, Amodiaquine; CYP2C9, Diclofenac; CYP2C19, (S)-Mephenytoin; CYP2D6, Dextromethorphan; CYP3A, Testosterone and Midazolam

[7] (The rate of increase in the aceneuramic acid group – 1) / (the rate of increase in the positive control group – 1) × 100.

concentration of unchanged aceneuramic acid in the digestive tract was 25.9 mmol/L (2 g [single dose]/250 mL).

(d) Transport by drug transporters

The membrane permeability of aceneuramic acid (100 μmol/L) was investigated using MDCKII cells engineered to express human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). The efflux ratio (permeability coefficient from the apical surface to the basolateral surface [Papp $_{A→B}$] to permeability coefficient from the basolateral surface to the apical surface [Papp $_{B→A}$]) was 0.914 in P-gp-expressing cells and 0.689 in BCRP-expressing cells, showing no clear difference from the efflux ratio (0.983 and 0.925, respectively) in the presence of the inhibitor of each transporter,[8)] which suggested that aceneuramic acid is not a substrate of either P-gp or BCRP (Reference CTD 4.2.2.6-3).

Organic cation transporter (OCT)1-mediated transport of aceneuramic acid (100 μmol/L) was investigated using human embryonic kidney 293 (HEK293) cells engineered to express human OCT1. While the ratio of intracellular uptake of aceneuramic acid in OCT1-expressing cells to that in OCT1-non-expressing cells (control cells) was 2.39, the ratio decreased to 1.55 in the presence of OCT1 inhibitor (quinidine at 100 μmol/L), suggesting that aceneuramic acid is a substrate of OCT1 (Reference CTD 4.2.2.6-4).

(e) Inhibition of drug transporters

The inhibitory effect of aceneuramic acid (at 400 and 4000 μmol/L) on the transport of the substrates[9)] of P-gp and BCRP was investigated using Caco-2 cells or MDCKII cells engineered to express human BCRP. Aceneuramic acid did not significantly inhibit either of the transporters in the range of concentrations investigated (Reference CTD 4.2.2.6-3).

The inhibitory effect of aceneuramic acid (at 400 and 4000 μmol/L) on the transport of the substrate[10)] of each transporter was investigated using HEK293 cells engineered to express human organic anion transporting polypeptide (OATP)1B1 or OATP1B3. Aceneuramic acid did not significantly inhibit either of the transporters in the range of concentrations investigated (Reference CTD 4.2.2.6-3).

The inhibitory effect of aceneuramic acid (at 10-4000 μmol/L against OCT1 and at 10 and 100 μmol/L against other transporters) on the transport of substates[11)] of various transporters was investigated using HEK293 cells engineered to express human organic anion transporter (OAT)1, OAT3, OCT2, multidrug and toxin extrusion (MATE)1, MATE2-K, and OCT1. Aceneuramic acid at ≤1000 μmol/L did not inhibit OCT1 but showed inhibitory effects on OCT1 at ≥3000 μmol/L (27.3% and 44.8% at 3000 and 4000 μmol/L, respectively). Aceneuramic acid did not inhibit other transporters in the range of concentrations investigated (References CTD 4.2.2.6-3 and 4.2.2.6-4).

8) P-gp, Valspodar; BCRP, Ko143
9) P-gp, Digoxin; BCRP, Prazosin
10) OATP1B1 and OATP1B3, Estradiol-17-b-glucuronide
11) OAT1, p-Aminohippuric acid; OAT3, Estrone-3-sulfate; OCT2, MATE1, and MATE2-K, Metformin; OCT1, Tetraethylammonium bromide

6.2.2 Studies in patients

6.2.2.1 Japanese phase I study (1) (CTD 5.3.3.2-1, Sialic Acid-1 study)

This study was conducted to investigate the pharmacokinetics and other aspects of aceneuramic acid in Japanese patients with DMRV (patients included in the pharmacokinetic analysis; 6 patients in Stage 1 and 3 patients in Stage 2). In Stage 1, subjects orally received aceneuramic acid 800 mg (immediate-release tablets) in a single dose or three times a day and, in Stage 2, subjects orally received aceneuramic acid 800 mg (immediate-release tablets) three times daily for 5 days. None of the subjects had an increase in the total aceneuramic acid concentration in serum from the baseline level (approximately 600 μg/mL) of the administration of aceneuramic acid immediate-release tablets. The total aceneuramic acid (mean value) excreted in urine within 24 hours post-dose increased by 33.0% in patients receiving aceneuramic acid in a single dose in Stage 1, by 77.0% in patients receiving aceneuramic acid three times a day in Stage 1, and by 38.1% in patients receiving aceneuramic acid in multiple doses in Stage 2 (on Day 5), suggesting the absorption of aceneuramic acid into the systemic circulation.

In the body, aceneuramic acid present as part of the carbohydrate chains bound to glycoproteins and glycolipids far outnumbers free aceneuramic acid, possibly resulting in the failure to evaluate the increase in the total serum aceneuramic acid concentration (sum of free aceneuramic acid and bound aceneuramic acid concentrations) after the oral administration of aceneuramic acid. To allow more sensitive evaluation of the increase in serum aceneuramic acid concentration after the administration of aceneuramic acid, the concentration of free aceneuramic acid in serum was evaluated in subsequent clinical studies.

6.2.2.2 Foreign phase I study (Reference CTD 5.3.3.2-3, Study CL101)

This study was conducted to investigate the pharmacokinetics and other aspects of aceneuramic acid in non-Japanese patients with DMRV (26 patients included in the pharmacokinetic analysis). In the single-dose part, subjects orally received aceneuramic acid (650 mg, 1950 mg, 2925 mg, 4875 mg, 6000 mg) as a single dose under fasting or postprandial conditions and, in the multiple-dose part, subjects orally received aceneuramic acid (650 mg, 975 mg, 1625 mg, or 2000 mg) three times daily for 7 days.

The pharmacokinetic parameters of serum free aceneuramic acid, corrected for pre-dose concentration in the single-dose part, are as shown in Section 6.1.1.

Table 13 shows the pharmacokinetic parameters of serum free aceneuramic acid on Day 7 in the multiple-dose part, corrected for pre-dose concentration of three times daily dosing for 7 days in the multiple-dose part.

Table 13. Pharmacokinetic parameters of serum free aceneuramic acid on Day 7 in the multiple-dose part, corrected for pre-dose concentration, following three times daily dosing of aceneuramic acid for 7 days

Dose	No. of subjects evaluated	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24} (μg•h/mL)	$t_{1/2}$ (h)
650 mg	8	0.170 (47.6)	20.0 [16.0, 24.0]	2.05 (54.6)	-
975 mg	8	0.230 (37.4)	20.0 [0, 24.0]	2.97 (25.5)	3.61[a)]
1625 mg	5	0.508 (30.3)	16.1 [4.08, 20.0]	6.70 (34.5)	-
2000 mg	6	0.436 (54.3)	20.0 [0, 24.0]	5.95 (51.7)	-

C_{max} and AUC_{0-24}, Geometric means (CV, %); t_{max}, Median [range]; -, Not calculated
The pharmacokinetic parameters were calculated using the values at each sampling point, subtracting the values at the same time point on the day before the administration of aceneuramic acid in the single-dose part (if the values at the same time point were not available, the average of all values on the day before the first dose of aceneuramic acid was used). If the corrected values were negative, they were treated as zero.
a) N = 1

6.2.2.3 Japanese phase I study (2) (CTD 5.3.3.2-2, Sialic Acid-2 study)

Table 14 shows the pharmacokinetic parameters of serum free aceneuramic acid, corrected for pre-dose concentration, in Japanese patients with DMRV (patients included in the pharmacokinetic analysis; 6 patients in Stage 1 and 3 patients in Stage 2) receiving aceneuramic acid orally [see Section 7.1.1 for the dosage regimen]. The mean level of free aceneuramic acid excreted in urine within 24 hours post-dose increased from the baseline level in all subjects, by 64.1% in the single dose group in Stage 1, by 766% in the three times daily dosing group in Stage 1, and by 191% in the multiple-dose group in Stage 2 (on Day 7).

Table 14. Pharmacokinetic parameters of serum free aceneuramic acid, corrected for pre-dose concentration, in subjects receiving aceneuramic acid

	Dosage regimen		No. of subjects evaluated	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0-24\,h}$ (μg•h/mL)
Stage 1	2 g as a single dose		3	0.276 (110.8) 0.319 [0.106, 0.624]	2.0 [1, 4]	1.831 (33.0) 2.074 [1.271, 2.328]
	2 g three times a day		3	0.195 (72.2) 0.233 [0.095, 0.335]	4.0 [2, 6]	0.975 (114.9) 1.343 [0.346, 1.991]
Stage 2	2 g three times daily for 7 days	Day 1	3	0.139 (36.0) 0.169 [0.093, 0.172]	6.0 [4, 8]	0.670 (36.6) 0.549 [0.544, 1.010]
		Day 7		0.213 (35.6) 0.234 [0.146, 0.285]	0 [0, 6]	1.315 (26.6) 1.276 [1.029, 1.731]

Upper row, Geometric mean (CV, %); lower row, Median [range]
a) Median [range]
The pharmacokinetic parameters were calculated using the values at each sampling point, subtracting the values at the same time point on the day before the administration of aceneuramic acid in each stage (if the values at the same time point were not available, the average of all values on the day before the first dose of aceneuramic acid was used). If the corrected values were negative, they were treated as zero.

6.2.2.4 Foreign phase II study (Reference CTD 5.3.5.1-3, Study CL201)

Table 15 shows trough free aceneuramic acid concentration in the serum of non-Japanese patients with DMRV (47 patients included in the pharmacokinetic analysis) orally receiving placebo or aceneuramic acid 1 or 2 g three times daily after meals [see Section 7.2.1 for the dosage regimen].

Table 15. Trough free aceneuramic acid concentration following the administration of placebo or aceneuramic acid

Treatment	Baseline	Week 6	Week 12	Week 18	Week 24 [a)]	Week 32	Week 40	Week 48
Placebo-aceneuramic acid 1 g	0.166 ± 0.028 (5)	0.152 ± 0.036 (5)	0.148 ± 0.029 (5)	0.151 ± 0.047 (5)	0.172 ± 0.062 (5)	0.253 ± 0.064 (5)	0.247 ± 0.083 (5)	0.320 ± 0.120 (5)
Placebo-aceneuramic acid 2 g	0.168 ± 0.027 (9)	0.156 ± 0.027 (9)	0.168 ± 0.028 (9)	0.164 ± 0.035 (9)	0.162 ± 0.025 (9)	0.343 ± 0.107 (9)	0.396 ± 0.133 (9)	0.332 ± 0.145 (9)
Aceneuramic acid 1 g	0.171 ± 0.037 (18)	0.298 ± 0.111 (18)	0.313 ± 0.176 (18)	0.256 ± 0.096 (16)	0.276 ± 0.077 (17)	0.286 ± 0.093 (17)	0.365 ± 0.334 (17)	0.318 ± 0.144 (17)
Aceneuramic acid 2 g	0.160 ± 0.024 (15)	0.369 ± 0.129 (15)	0.428 ± 0.194 (15)	0.380 ± 0.173 (15)	0.384 ± 0.124 (14)	0.379 ± 0.150 (15)	0.359 ± 0.111 (15)	0.415 ± 0.179 (15)

Unit, μg/mL; Mean ± SD (number of subjects evaluated)

a) Data from subjects who received placebo in the placebo-aceneuramic acid 1 g group or placebo-aceneuramic acid 2 g group up to Week 24

6.2.2.5 Japanese phase III study (1) (CTD 5.3.5.1-1, Sialic acid-3 study)

Table 16 shows trough free aceneuramic acid concentration in the serum of Japanese patients with DMRV (19 patients included in the pharmacokinetic analysis [4 in the placebo group, 15 in the aceneuramic acid group]) orally receiving placebo or aceneuramic acid 2 g three times daily after meals [for the dosage regimen, see Section 7.3.1].

Table 16. Trough free aceneuramic acid concentration in serum in subjects receiving placebo or aceneuramic acid

Treatment	No. of subjects evaluated	Baseline	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48
Placebo	4	0.149 ± 0.029	0.150 ± 0.041	0.174 ± 0.040	0.149 ± 0.034	0.146 ± 0.033	0.145 ± 0.023	0.147 ± 0.031
Aceneuramic acid	15	0.150 ± 0.058	0.423 ± 0.154	0.529 ± 0.194	0.397 ± 0.163	0.450 ± 0.199	0.465 ± 0.144	0.543 ± 0.425

Unit, μg/mL; Mean ± SD

6.2.2.6 Japanese phase III study (2) and foreign phase III study (CTD 5.3.5.1-2, Study NPC-09-1 and Reference CTD 5.3.5.1-4, Study CL301)

Table 17 shows trough free aceneuramic acid concentration at Week 48 in the serum of Japanese and non-Japanese patients with DMRV orally receiving multiple doses of aceneuramic acid 2 g three times daily after meals.

Table 17. Free aceneuramic acid concentration in serum at Week 48 in the Japanese phase III study (2) and in the foreign phase III study

Study	Population	Baseline	Week 48
Japanese phase III study (2)	Japanese	0.096 ± 0.018 (10)	0.210 ± 0.051 (9)
Foreign phase III study	Non-Japanese	0.160 ± 0.032 (45)	0.300 ± 0.131 (42)

Unit, μg/mL; Mean ± SD (number of subjects evaluated)

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics of aceneuramic acid

The applicant's explanation about the pharmacokinetics of aceneuramic acid in patients with DMRV:

In patients with DMRV, the decreased biosynthesis of sialic acids such as aceneuramic acid results in the reduced level of sialic acid in muscle tissues (*J Biol Chem.* 2004;279:11402-7). The mean serum free aceneuramic acid level in patients with DMRV who did not receive aceneuramic acid (0.135 μg/mL[12)]) tended to be lower than that in healthy adults (0.203 μg/mL[13)]). In the Japanese

12) The mean serum free aceneuramic acid concentration measured within 30 minutes before the initial dose in 6 subjects in the Japanese phase I study (2) (Sialic Acid-2 study).

phase III studies (Sialic Acid-3 study and Study NPC-09-1) in patients with DMRV, the trough serum free aceneuramic acid concentration increased by 2- to 3-fold in patients orally receiving aceneuramic acid 2 g three times daily, reaching the level higher than, or equivalent to, the mean serum free aceneuramic acid concentration in healthy adults. The above results suggest that oral administration of aceneuramic acid 2 g three times daily supplements sialic acid depleted in patients with DMRV.

In patients receiving aceneuramic acid 6000 mg (in the form of 500 mg extended-release tablets) in the foreign phase I study (Study CL101), t_{max} was delayed and AUC increased following the administration of aceneuramic acid under postprandial conditions, compared to that under fasting conditions, for the mean serum free aceneuramic acid concentration [see Section 6.1.1]. The results suggest that oral administration of aceneuramic acid under postprandial conditions can provide a more sustained sialic acid supplementation compared to that under fasting conditions.

PMDA's view:
The Japanese phase I study (2) (Sialic Acid-2 study) showed an increase in urinary free aceneuramic acid concentration following the administration of aceneuramic acid, and the Japanese and foreign clinical studies demonstrated that oral administration of aceneuramic acid 2 g three times daily under postprandial conditions increased the serum free aceneuramic acid concentration in patients with DMRV. These findings have confirmed that aceneuramic acid is absorbed when administered orally. Based on the above results, the outcomes are consistent with the development concept of aceneuramic acid, where the administration of aceneuramic acid serves to supplement sialic acid depleted in the muscle tissues of patients with DMRV.

6.R.2 Effects of aceneuramic acid on QT/QTc interval prolongation

No studies have been conducted to evaluate the effects of aceneuramic acid on the QT/corrected QT (QTc) interval. PMDA asked the applicant to explain the effects of aceneuramic acid on the QT/QTc interval.

The applicant's explanation:
No cardiovascular risk of aceneuramic acid was observed either in the non-clinical safety pharmacology studies on the effects of aceneuramic acid on blood pressure, heart rate, and electrocardiogram in dogs, or in the human ether-a-go-go related gene (hERG) study [see Section 3.2].

In the Japanese phase III study (1) (Sialic Acid-3 study) and the Japanese long-term treatment study (Sialic Acid-4 study), the QT/QTc interval prolongation effect of aceneuramic acid was evaluated. In the Japanese phase III study (1), QTcF >450 ms was observed in 2 subjects, and changes from baseline in QTcF >30 ms were observed in 1 subject. In the Japanese long-term treatment study, changes from baseline in QTcF >30 ms were observed in 1 subject. All of the above observations were transient fluctuations.

[13)] In the foreign phase I study (Study CL101), the serum free aceneuramic acid concentration was measured in 47 healthy adults when aceneuramic acid was not administered.

Furthermore, the data obtained from the Japanese clinical studies were used to investigate a relationship between serum free aceneuramic acid concentrations and QTcF. The results showed no clear correlation (correlation coefficient = 0.187). In the Japanese phase III studies (Sialic Acid-3 study, Study NPC-09-1, and Sialic Acid-4 study) including the Japanese long-term treatment study, as well as in the foreign phase III study (Study CL301), no adverse events related to QT interval prolongation were noted in subjects treated with aceneuramic acid.

Based on the above, the applicant considered that aceneuramic acid has a low risk of QT/QTc interval prolongation and proarrhythmic effects.

PMDA concluded that the study results presented no significant concerns about the risk of proarrhythmia in patients treated with aceneuramic acid at the clinical dose.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of clinical studies shown in Table 18 as the primary efficacy and safety data.

Table 18. List of clinical studies on efficacy and safety

Data category	Region	Study CTD	Phase	Study population	No. of patients treated	Dosage regimen	Main endpoints
Evaluation	Japan	Sialic Acid-1 study 5.3.3.2-1	I	Patients with DMRV	6	Stage 1: Oral administration of aceneuramic acid 800 mg (immediate-release tablet) as a single dose or three times a day Stage 2: Oral administration of aceneuramic acid 800 mg (immediate-release tablet) three times daily for 5 days	Safety Pharmacokinetics
	Japan	Sialic Acid-2 study 5.3.3.2-2	I	Patients with DMRV	6	Stage 1: Oral administration of aceneuramic acid 2 g as a single dose or three times a day Stage 2: Oral administration of aceneuramic acid 2 g three times daily for 7 days	Safety Pharmacokinetics
	Japan	Sialic Acid-3 study 5.3.5.1-1	III	Patients with DMRV	20	Oral administration of placebo or aceneuramic acid 2 g three times daily	Efficacy Safety
	Japan	Study NPC-09-1 5.3.5.1-2	III	Patients with DMRV	14	Oral administration of placebo or aceneuramic acid 2 g three times daily	Efficacy Safety
	Japan	Sialic Acid-4 study 5.3.5.2-1	III	Patients with DMRV	19	Oral administration of aceneuramic acid 2 g three times daily	Efficacy Safety
Reference	Foreign	Study CL101 5.3.3.2-3	I	Patients with DMRV	26	Single-dose part: Single oral administration of aceneuramic acid 650, 1950, 2925, 4875, or 6000 mg Multiple-dose part: Oral administration of aceneuramic acid l 650, 975, 1625, or 2000 mg 3 times daily for 7 days	Safety Pharmacokinetics
	Foreign	Study CL201 5.3.5.1-3	II	Patients with DMRV	47	Oral administration of placebo or aceneuramic acid 1 or 2 g three times daily	Efficacy Safety
	Foreign	Study CL301 5.3.5.1-4	III	Patients with DMRV	89	Oral administration of placebo or aceneuramic acid 2 g three times daily	Efficacy Safety

Below are described the key study results.

7.1 Phase I studies

7.1.1 Japanese phase I study (2) (CTD 5.3.3.2-2, Sialic Acid-2 study [September 2013 to January 2015])

A two-stage study was conducted to evaluate the safety and other aspects of aceneuramic acid in Japanese patients with DMRV with mutations in the *GNE* gene (target sample size; 6 subjects in Stage 1 and 3 subjects in Stage 2). In Stage 1, the first 3 enrolled subjects received a single oral dose of aceneuramic acid 2 g under fasting conditions, and the next 3 subjects received aceneuramic acid 2 g orally three times a day, with a dosing interval of 6 to 8 hours. In Stage 2, subjects enrolled in Stage 1 received aceneuramic acid 2 g orally three times daily for 7 days, with a dosing interval of 6 to 8 hours.

All of 9 subjects who received the study drug (6 in Stage 1 and 3 in Stage 2) were included in the safety analysis set. No study discontinuation occurred.

Adverse events were reported in 1 of 3 subjects receiving aceneuramic acid as a single dose in Stage 1, in 2 of 3 subjects receiving aceneuramic acid three times a day in Stage 1, and in 2 of 3 subjects in Stage 2. No serious adverse events (including deaths) or adverse events leading to discontinuation of the study drug were reported. Adverse events reported by ≥2 subjects were blood triglycerides increased (0 subjects receiving aceneuramic acid as a single dose in Stage 1, 2 subjects receiving aceneuramic acid three times a day in Stage 1, and 1 subject receiving multiple doses of aceneuramic acid in Stage 2).

7.2 Phase II studies

7.2.1 Foreign phase II study (Reference CTD 5.3.5.1-3, Study CL201 [June 2012 to October 2013])

A randomized, double-blind, parallel-group study was conducted in the US and Israel to evaluate the safety, efficacy, and other aspects of aceneuramic acid in non-Japanese patients with DMRV aged ≥18 and ≤65 years with mutations in the *GNE* gene (target sample size, 45 subjects[14] [≥60% of subjects were required to be able to walk ≥200 m in the 6-minute walk test at the time of enrollment]).

The key inclusion criteria were as follows: Patients who had reproducible results for elbow flexor and knee extensor muscle strength measured by a dynamometer at screening,[15] and who were able to walk ≥20 m (use of orthotics and assistive devices allowed).

The study consisted of a screening period (up to 4 weeks), a placebo-controlled period (24 weeks), an extension period (24 weeks), and a follow-up period (4 weeks).

During the placebo-controlled period, subjects orally received either placebo or aceneuramic acid 1 or 2 g three times daily after meals. During the extension period, subjects orally received aceneuramic acid 1 or 2 g three times daily after meals, with a recommended dosing interval of approximately 8 hours. Subjects assigned to the aceneuramic acid 1 or 2 g group during the placebo-controlled period

[14] The sample size required for evaluation of the pharmacokinetics of aceneuramic acid was 15 subjects per group.
[15] The difference between the 2 unilateral measurements of muscle strength for the elbow extensor and knee extensor muscles in the subjects was <15%.

had to continue the same dose during the extension period. Subjects assigned to the placebo group during the placebo-controlled period were randomly assigned to the aceneuramic acid 1 or 2 g group at the entry into the extension period.

All of 47 subjects who were randomized during the placebo-controlled period[16] (14 in the placebo group, 18 in the aceneuramic acid 1 g group, 15 in the aceneuramic acid 2 g group) and 46 subjects who entered the extension period (5 in the placebo-aceneuramic acid 1 g group, 9 in the placebo-aceneuramic acid 2 g group, 17 in the aceneuramic acid 1 g group, 15 in the aceneuramic acid 2 g group) were included in the safety and efficacy analysis sets. Treatment discontinuation occurred in 1 subject in the aceneuramic acid 1 g group during the placebo-controlled period due to an adverse event.

Table 19 shows changes from baseline in the total upper limb muscle strength score[17][18] or the total lower limb muscle strength score[19] at Week 24 (end of the placebo-controlled period), the primary efficacy endpoint. Table 20 shows the changes from baseline in these scores at Week 48 (end of the extension period) in subjects who entered the extension period.

Table 19. Changes from baseline in total upper or lower limb muscle strength score at Week 24 (efficacy analysis population)

	Treatment	Baseline	Week 24	Change[a) b)]	Between-group difference in change[a) c)]
Total upper limb muscle strength score	Placebo	35.92 ± 15.42 (14)	33.17 ± 15.62 (13)	−1.66 ± 0.85	
	Aceneuramic acid 1 g	37.86 ± 17.03 (18)	35.76 ± 17.81 (17)	−1.07 ± 0.86	0.59 [−1.74, 2.92]
	Aceneuramic acid 2 g	48.51 ± 31.58 (15)	49.66 ± 34.55 (15)	0.67 ± 0.75	2.33 [0.11, 4.55]
Total lower limb muscle strength score	Placebo	34.68 ± 23.52 (14)	35.23 ± 25.78 (14)	0.79 ± 1.45	
	Aceneuramic acid 1 g	29.44 ± 18.28 (17)	29.26 ± 19.81 (16)	2.30 ± 1.23	1.52 [−2.34, 5.38]
	Aceneuramic acid 2 g	45.69 ± 31.29 (15)	49.18 ± 37.94 (15)	1.85 ± 1.74	1.06 [−3.04, 5.17]

Unit, kg; Mean ± SD (number of subjects evaluated)

a) Calculated by generalized estimating equation (GEE) model using change from baseline as the dependent variable; treatment group, time point (6, 12, 18, and 24 weeks), and the interaction term between treatment group and time point as fixed effects; and baseline value, age, and sex as covariates.

b) Least-squares mean ± standard error (SE)

c) Intergroup differences in least squares mean values between the aceneuramic acid 1g or 2g groups and the placebo group [95% confidence interval (CI)].

16) Randomization was stratified based on whether subjects could walk ≥200 m in the 6-minute walk test.

17) The total upper limb muscle strength score was calculated by measuring the muscle strength of the grip, shoulder abductors, elbow flexors, and elbow extensors on both sides using a dynamometer and by summing the mean values (kg) for strength of the 4 muscle groups.

18) Grip strength was read in 2 kg increments.

19) The total lower limb muscle strength score was calculated by measuring the muscle strength of the hip adductors, hip abductors, hip flexors, hip extensors, and knee flexors on both sides using a dynamometer and by summing the mean values (kg) for strength of the 5 muscle groups.

Table 20. Changes from baseline in total upper or lower limb muscle strength score up to Week 48 (efficacy analysis population)

	Treatment group	Baseline	Change from baseline	
			Week 24[a)]	Week 48
Total upper limb muscle strength score	Placebo-Aceneuramic acid 1 g	36.39 ± 15.94 (5)	−4.04 ± 3.39 (5)	−4.71 ± 2.70 (5)
	Placebo-Aceneuramic acid 2 g	35.66 ± 16.10 (9)	−0.64 ± 2.21 (8)	−0.15 ± 1.95 (7)
	Aceneuramic acid 1 g	37.86 ± 17.03 (18)	−1.14 ± 3.53 (17)	−2.52 ± 5.56 (17)
	Aceneuramic acid 2 g	48.51 ± 31.58 (15)	1.15 ± 4.15 (15)	0.89 ± 6.14 (15)
Total lower limb muscle strength score	Placebo-Aceneuramic acid 1 g	33.17 ± 20.51 (5)	−2.63 ± 3.13 (5)	−2.42 ± 4.14 (5)
	Placebo-Aceneuramic acid 2 g	35.52 ± 26.20 (9)	2.31 ± 5.87 (9)	0.72 ± 8.48 (9)
	Aceneuramic acid 1 g	29.44 ± 18.28 (17)	1.29 ± 4.86 (16)	0.65 ± 5.18 (16)
	Aceneuramic acid 2 g	45.69 ± 31.29 (15)	3.49 ± 9.46 (15)	2.44 ± 10.21 (15)

Unit, kg; Mean ± SD (number of subjects evaluated)

a) Data from the subjects who received placebo in the placebo-aceneuramic acid 1 g group or the placebo-aceneuramic acid 2 g group at Week 24.

Table 21 shows the proportion of subjects with any adverse event and the incidence of adverse events reported in ≥2 subjects in any group up to Week 24 (placebo-controlled period) or Week 48 (extension period).

Table 21. Proportion of subjects with any adverse event and incidence of adverse events reported in ≥2 subjects in any group (safety analysis set)

	Up to Week 24 (placebo-controlled period)			Up to Week 48 (extension period)[a)]			
	Placebo	Aceneuramic acid 1 g	Aceneuramic acid 2 g	Placebo-Aceneuramic acid 1 g	Placebo-Aceneuramic acid 2 g	Aceneuramic acid 1 g	Aceneuramic acid 2 g
N	14	18	15	5	9	18	15
Any adverse event	13 (92.9)	18 (100)	15 (100)	5 (100)	9 (100)	18 (100)	15 (100)
Adverse events reported in ≥2 subjects in any group							
Procedural pain	4 (28.6)	8 (44.4)	6 (40.0)	3 (60.0)	5 (55.6)	13 (72.2)	13 (86.7)
Headache	5 (35.7)	4 (22.2)	5 (33.3)	3 (60.0)	5 (55.6)	5 (27.8)	6 (40.0)
Diarrhoea	0	6 (33.3)	4 (26.7)	0	0	6 (33.3)	5 (33.3)
Myalgia	2 (14.3)	1 (5.6)	4 (26.7)	2 (40.0)	1 (11.1)	2 (11.1)	5 (33.3)
Fatigue	2 (14.3)	3 (16.7)	3 (20.0)	3 (60.0)	2 (22.2)	6 (33.3)	5 (33.3)
Abdominal pain	1 (7.1)	3 (16.7)	3 (20.0)	0	1 (11.1)	3 (16.7)	4 (26.7)
Pain in extremity	4 (28.6)	2 (11.1)	3 (20.0)	3 (60.0)	1 (11.1)	2 (11.1)	3 (20.0)
Nasal congestion	2 (14.3)	2 (11.1)	3 (20.0)	1 (20.0)	1 (11.1)	3 (16.7)	5 (33.3)
Flatulence	2 (14.3)	2 (11.1)	3 (20.0)	1 (20.0)	1 (11.1)	3 (16.7)	4 (26.7)
Contusion	2 (14.3)	2 (11.1)	3 (20.0)	0	2 (22.2)	3 (16.7)	3 (20.0)
Arthralgia	4 (28.6)	7 (38.9)	2 (13.3)	3 (60.0)	1 (11.1)	7 (38.9)	6 (40.0)
Back pain	4 (28.6)	5 (27.8)	2 (13.3)	2 (40.0)	3 (33.3)	7 (38.9)	4 (26.7)
Influenza like illness	3 (21.4)	2 (11.1)	2 (13.3)	2 (40.0)	1 (11.1)	3 (16.7)	4 (26.7)
Fall	2 (14.3)	2 (11.1)	2 (13.3)	1 (20.0)	1 (11.1)	3 (16.7)	2 (13.3)
Upper respiratory tract infection	1 (7.1)	2 (11.1)	2 (13.3)	1 (20.0)	0	2 (11.1)	2 (13.3)
Paraesthesia	1 (7.1)	0	2 (13.3)	1 (20.0)	2 (22.2)	0	2 (13.3)
Pharyngitis	1 (7.1)	0	2 (13.3)	0	2 (22.2)	2 (11.1)	2 (13.3)
Abdominal distension	0	0	2 (13.3)	0	0	0	2 (13.3)
Muscle strain	0	0	2 (13.3)	0	0	0	2 (13.3)
Cerumen impaction	0	0	2 (13.3)	0	0	0	2 (13.3)
Dizziness	1 (7.1)	4 (22.2)	1 (6.7)	1 (20.0)	0	4 (22.2)	1 (6.7)
Musculoskeletal pain	3 (21.4)	2 (11.1)	1 (6.7)	1 (20.0)	2 (22.2)	4 (22.2)	3 (20.0)
Dyspepsia	2 (14.3)	2 (11.1)	1 (6.7)	3 (20.0)	0	4 (22.2)	1 (6.7)
Liver function test abnormal	0	2 (11.1)	1 (6.7)	0	0	2 (11.1)	2 (13.3)
Nasopharyngitis	4 (28.6)	1 (5.6)	1 (6.7)	2 (40.0)	3 (33.3)	4 (22.2)	1 (6.7)
Nausea	2 (14.3)	1 (5.6)	1 (6.7)	1 (20.0)	1 (11.1)	3 (16.7)	2 (13.3)
Vomiting	0	1 (5.6)	1 (6.7)	0	0	2 (11.1)	2 (13.3)
Oedema peripheral	1 (7.1)	1 (5.6)	1 (6.7)	1 (20.0)	1 (11.1)	1 (5.6)	2 (13.3)
Pain	1 (7.1)	1 (5.6)	1 (6.7)	0	2 (22.2)	2 (11.1)	1 (6.7)
Rhinorrhoea	1 (7.1)	0	1 (6.7)	0	1 (11.1)	1 (5.6)	3 (20.0)
Haematoma	0	0	1 (6.7)	0	0	1 (5.6)	2 (13.3)
Musculoskeletal stiffness	0	0	1 (6.7)	0	0	0	2 (13.3)
Muscular weakness	0	3 (16.7)	0	0	0	3 (16.7)	0
Rash	1 (7.1)	2 (11.1)	0	1 (20.0)	0	3 (16.7)	2 (13.3)
Hypoaesthesia	0	2 (11.1)	0	0	0	2 (11.1)	1 (6.7)
Abdominal discomfort	0	2 (11.1)	0	1 (20.0)	0	2 (11.1)	0
Constipation	0	2 (11.1)	0	0	0	2 (11.1)	0
Abdominal pain upper	0	1 (5.6)	0	0	0	2 (11.1)	1 (6.7)
Post procedural haematoma	0	1 (5.6)	0	1 (20.0)	0	2 (11.1)	0
Oropharyngeal pain	3 (21.4)	1 (5.6)	0	3 (60.0)	2 (22.2)	1 (5.6)	2 (13.3)
Inguinal pain	2 (14.3)	1 (5.6)	0	1 (20.0)	1 (11.1)	1 (5.6)	0
Depression	2 (14.3)	1 (5.6)	0	0	2 (22.2)	3 (16.7)	0
Insomnia	2 (14.3)	1 (5.6)	0	2 (40.0)	0	1 (5.6)	0
Anxiety	1 (7.1)	0	0	0	1 (11.1)	3 (16.7)	2 (13.3)
Dysaesthesia	1 (7.1)	0	0	0	2 (22.2)	2 (11.1)	1 (6.7)
Urinary tract infection	0	0	0	0	1 (11.1)	2 (11.1)	0
Toothache	1 (7.1)	0	0	0	2 (22.2)	1 (5.6)	0
Cough	3 (21.4)	0	0	1 (20.0)	2 (22.2)	0	0
Dysuria	0	0	0	2 (40.0)	0	0	0

n (%)

a) Includes adverse events reported up to Week 24.

No serious adverse events, including deaths, were reported. Adverse events leading to treatment discontinuation occurred in 1 of 18 subjects (hepatic enzyme abnormal) in the aceneuramic acid 1 g group during the placebo-controlled period, and its causal relationship to the study drug could not be ruled out.

7.3 Phase III study

7.3.1 Japanese phase III study (1) (CTD 5.3.5.1-1, Sialic Acid-3 study [March 2016 to July 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and other aspects of aceneuramic acid in Japanese patients with DMRV aged ≥20 and ≤50 years with mutations in the *GNE* gene (target sample size, ≥20 subjects[20)] [including ≥15 patients[21)] who could walk ≥200 m in the 6-minute-walk test without walking aids such as canes or walkers[22)] at enrollment]; 4 in the placebo group, 16 in the aceneuramic acid group).

The key inclusion criterion was as follows: Patients with reproducible results for elbow extensor muscle strength measured by a dynamometer at screening.[23)]

The study consisted of a screening period (up to 4 weeks), a treatment period (48 weeks), and a follow-up period (4 weeks[24)]).

Subjects orally received placebo or aceneuramic acid 2 g three times daily after meals, with a recommended dosing interval of approximately 8 hours.

All of 20 randomized patients[25)] (4 in the placebo group, 16 in the aceneuramic acid group) were included in the safety analysis set. Of the 20 subjects, 19 subjects (4 in the placebo group, 15 in the aceneuramic acid group) were included in the full analysis set (FAS), and the FAS was used for the primary analysis. The remaining 1 subject in the aceneuramic acid group was excluded because no efficacy evaluation data after the administration of study drug were available. Treatment discontinuation occurred in 1 subject in the aceneuramic acid group due to pregnancy.

Table 22 shows the changes from baseline in the total upper limb muscle strength score[17)18)] at Week 48, the primary efficacy endpoint.

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20) The target sample size was determined from the perspective of feasibility of the study.
21) At enrollment, the proportion of patients able to walk ≥200 m in the 6-minute walking test was balanced so that neither gender exceeded 60%.
22) Ankle-foot orthoses were allowed.
23) The difference between 2 measurements of muscle strength in the dominant hand was <15%.
24) The follow-up period was omitted in subjects who entered the Japanese long-term treatment study (CTD 5.3.5.2-1, Sialic Acid-4 study).
25) Subjects were stratified based on their ability to walk ≥200 m in the 6-minute- walk test, and then randomly assigned to the placebo group or the treatment group in a 1:4 ratio.

Table 22. Changes from baseline in total upper limb muscle strength score at Week 48 (FAS, last observation carried forward [LOCF])

Treatment	No. of subjects evaluated	Baseline	Week 48	Change[a) b)]	Between-group difference in change[b)] [95% CI]
Placebo	4	46.04 ± 22.75	40.96 ± 20.70	−6.18 ± 2.92	
Aceneuramic acid	15	31.50 ± 14.56	31.41 ± 15.22	−1.40 ± 2.11	4.78 [−0.31, 9.87]

Unit, kg; Mean ± SD
To calculate the total muscle strength score, a missing value for muscle strength on one side of the body was replaced with the value measured on the opposite side.
a) Least squares mean ± SE
b) Analysis of covariance with the change up to the final assessment point at Week 48 or earlier as the response variable, baseline value as the covariate, and treatment group, gender, and 6-minute walk test (<200 m, ≥200 m) as explanatory variables.

Table 23 shows the proportion of subjects with any adverse event and the incidence of adverse events reported in ≥2 subjects in either group.

Table 23. Proportion of subjects with any adverse events and incidence of adverse events reported in ≥2 subjects in either group (safety analysis set)

	Placebo	Aceneuramic acid
N	4	16
Any adverse event	3 (75.0)	14 (87.5)
Adverse events reported in ≥2 subjects in either group		
Viral upper respiratory tract infection	1 (25.0)	7 (43.8)
Fall	1 (25.0)	4 (25.0)
Contusion	0	4 (25.0)
Headache	0	3 (18.8)
Pain in extremity	0	2 (12.5)
Gastroenteritis viral	0	2 (12.5)
Angular cheilitis	0	2 (12.5)
Influenza	0	2 (12.5)
Otitis externa	0	2 (12.5)
Excoriation	0	2 (12.5)

n (%)

No death occurred. A serious adverse event other than death was reported in 1 of 16 subjects in the aceneuramic acid group (foetal death), and its causal relationship to the study drug could not be ruled out. There were no adverse events leading to treatment discontinuation.

7.3.2 Japanese phase III study (2) (CTD 5.3.5.1-2, Study NPC-09-1 [February 2021 to March 2022])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and other aspects of aceneuramic acid in Japanese patients with DMRV aged ≥20 and ≤50 years with mutations the *GNE* gene (target sample size, 10 patients[26)] [3 in the placebo group, 7 in the aceneuramic acid group]).

The key inclusion criteria were as follows: Patients who had reproducible results for elbow extensor muscle strength measured by a dynamometer at screening,[27)] GNE myopathy Functional Activities

[26)] The target sample sized was determined from the perspective of feasibility of the study. The study was designed to include ≥5 new subjects who had not participated in neither the Japanese phase III study (Sialic Acid-3 study) nor the Japanese long-term treatent study (Sialic Acid-4 study), of whom, 1 or 2 subjects were planned to be assigned to the placebo group.
[27)] The difference between the 2 muscle strength measurements of the subjects' dominant hand was <15%.

Scale (GNEM-FAS[28)]) upper extremity score[29)] of ≥24 and a disease duration of ≥5 to ≤15 years, and confirmed upper extremity muscle weakness by manual muscle testing or grip strength measurements over the past few years. Additionally, the study included patients who had participated in the previous Japanese phase III study (1) (Sialic Acid-3 study) or the Japanese long-term treatment study (Sialic Acid-4 study) and had exhibited a decline in upper extremity muscle strength scores when the study drug was not administered after the end of the study.

This study consisted of a screening period (up to 4 weeks), a treatment period (48 weeks), and a follow-up period (4 weeks).

Subjects orally received placebo or aceneuramic acid 2 g three times daily after meals, with a recommended dosing interval of approximately 8 hours.

All of 14 randomized subjects (4 in the placebo group, 10 in the aceneuramic acid group) were included in the safety analysis set and the FAS. The FAS served as the population for primary analysis of efficacy. No treatment discontinuation occurred.

Table 24 shows the change from baseline in the total upper extremity muscle strength score[17)30)] at Week 48, the primary efficacy endpoint.

Table 24. Change from baseline in total upper limb muscle strength scores at Week 48 (FAS)

Treatment	No. of subjects evaluated	Baseline[a)]	Week 48	Change[b) c)]	Between-group difference in change[c)] [95% CI]
Placebo	4	26.55 ± 8.74	23.93 ± 8.23	−2.63 ± 1.73	
Aceneuramic acid	10	32.77 ± 12.37	32.66 ± 12.72	−0.12 ± 1.09	2.51 [−1.72, 6.74]

Unit, kg; Mean ± SD
To calculate the total muscle strength score, a missing value for muscle strength on one side was replaced with the value measured on the opposite side.
a) Although the protocol had specified that grip strength should be measured in units of 2 kg, there were 2 subjects with odd values for left-hand grip strength at baseline. In these subjects, the right-hand grip strength values were used instead of the mean of the measured values for both hands.
b) Least squares mean ± SE
c) Calculated by a linear mixed-effects model using the change from baseline as the objective variable; time points (Week 12, 24, 36, and 48), treatment group, and the interaction between time point and treatment group as fixed effects; and subjects as random effect. The variance-covariance matrix of within-subject effects was based on Variance Components.

Table 25 shows the proportion of subjects with any adverse events and the incidence of adverse events reported in ≥2 subjects in either group.

28) GNEM-FAS is a scale that assesses the impact of muscle strength changes on the functional status in patients with GNE myopathy (DMRV) (*J Comp Eff Res.* 2018;7:381-395). It consists of 10 items for motor function (equivalent to lower limb function assessment, total score of items 1 to 10 is 40 points), 8 items for upper limb function (total score of items 11 to 18 is 32 points), and 7 items for self-care (total score of items 19 to 25 is 28 points), with a total possible score of 100 points.

29) The GNEM-FAS upper limb section consists of 8 items (Item 11, making a fist; Item 12, writing with a pencil or pen; Item 13, bringing the hand to the mouth; Item 14, cutting food with utensils; Item 15, carrying objects; Item 16, opening a door; Item 17, opening a beverage bottle; Item 18, lifting objects overhead). Patients were assessed for each item on a scale point of 0 to 4 (0 = unable to perform or requires maximal assistance of person; 1 = requires slight to moderate assistance; 2 = requires assistive devices and/or external assistance; 3 = slow or slightly difficult, assistive devices allowed, no external assistance; 4 = no limitations, no compensatory action, no assistive devices), for a total score of 32 points.

30) With the hand dynamometer used in this study, values below 4 kg were treated as reference values. During the study, it was found that the handling of values below 4 kg varied among the participating study sites. Thus, values below 4 kg measured before or at Week 12 were treated as 0 kg in the primary analysis. According to the applicant, the change of the rule had no impact on the efficacy evaluation because the results of the primary analysis were the same as those obtained using the grip strength measurements by the study sites before or at Week 12.

Table 25. Proportion of subjects with any adverse events and incidence of adverse events reported in ≥2 subjects in either group (safety analysis set)

	Placebo	Aceneuramic acid
N	4	10
Any adverse event	4 (100)	9 (90.0)
Adverse events reported in ≥2 subjects in either group		
Immunisation reaction	1 (25.0)	3 (30.0)
Pyrexia	2 (50.0)	2 (20.0)
Nasopharyngitis	2 (50.0)	2 (20.0)
Diarrhoea	1 (25.0)	2 (20.0)
Dry eye	0	2 (20.0)
Gastrooesophageal reflux disease	0	2 (20.0)

n (%)

No death occurred. Serious adverse events other than death were reported in 1 of 4 subjects in the placebo group (papillary thyroid cancer) and in 1 of 10 subjects in the aceneuramic acid group (COVID-19). Their causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation.

7.3.3 Japanese long-term treatment study (CTD 5.3.5.2-1, Sialic Acid-4 study [March 2017 to January 2019])

An open-label, uncontrolled study was conducted to evaluate the long-term safety and efficacy, and other aspects of aceneuramic acid in subjects who had completed the Japanese phase III study (1) (Sialic Acid-3 study).

The study consisted of a treatment period (72 weeks) and a follow-up period (4 weeks).

Subjects orally received aceneuramic acid 2 g three times daily after meals, with the recommended dosing interval of approximately 8 hours.

A total of 19 subjects (4 in the placebo group, 15 in the aceneuramic acid group) who completed the Japanese phase III study (1) (Sialic Acid-3 study) were enrolled, and all of whom were included in both the safety and the efficacy analysis sets. One subject discontinued the study treatment at his/her own request.

Table 26 shows the change from the baseline of the Japanese phase III study (1) in the total upper limb muscle strength score[17)18)] at Week 72, the primary efficacy endpoint.

Table 26. Change from the baseline of Japanese phase III study (1) in total upper limb muscle strength score at final evaluation point of Japanese long-term treatment study (efficacy analysis set, LOCF)

Treatment group in Japanese phase III study (1)	Japanese phase III study (1)	Japanese long-term treatment study				Change at Week 72[b)]
	Baseline	Baseline	Week 24	Week 48	Week 72[a)]	
Placebo	46.04 ± 22.75 (4)	40.71 ± 20.69 (4)	38.94 ± 21.22 (4)	36.69 ± 20.93 (4)	37.94 ± 20.94 (4)	−8.10 ± 6.38
Aceneuramic acid	31.50 ± 14.56 (15)	31.41 ± 15.22 (15)	29.82 ± 13.70 (15)	28.63 ± 14.52 (14)	27.30 ± 12.95 (14)	−3.48 ± 4.90

Unit, kg; Mean ± SD (number of subjects evaluated)
To calculate the total muscle strength score, a missing value for muscle strength on one side was replaced with the value measured on the opposite side.
a) The period from the baseline (Week 0) of the Japanese phase III study (1) to Week 120
b) Change from the baseline of the Japanese phase III study (1) to Week 72 of the long-term treatment study (or to the last evaluation time point before Week 72)

The incidence of adverse events was 78.9% (15 of 19 subjects). Table 27 shows the incidences of adverse events reported in ≥2 subjects.

Table 27. Incidences of adverse events reported in ≥2 subjects (safety analysis set)

N	19
Viral upper respiratory tract infection	7 (36.8)
Fall	6 (31.6)
Contusion	4 (21.1)
Headache	2 (10.5)
Hypoaesthesia	2 (10.5)
Faeces soft	2 (10.5)
Arthralgia	2 (10.5)
Oedema peripheral	2 (10.5)

n (%)

No death occurred. A serious adverse event other than death was reported in 1 of 19 subjects in the aceneuramic acid group (large intestinal polypectomy), and its causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation.

7.3.4 Foreign phase III study (Reference CTD 5.3.5.1-4, Study CL301 [May 2015 to June 2017])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 7 countries[31)] to evaluate the efficacy, safety, and other aspects of aceneuramic acid in non-Japanese patients with DMRV aged ≥18 and ≤55 years with mutations in the *GNE* gene (target sample size, 80 patients[32)] [40 in the placebo group, 40 in the aceneuramic acid group[33)]]).

The key inclusion criteria were as follows: Patients with DMRV aged ≥18 and ≤55 years with confirmed mutations in the *GNE* gene, who had reproducible results for muscle strength of the elbow flexors[34)] measured by a dynamometer at screening, and who could walk ≥200 m in the 6-minute walk test without using walking aids such as canes or walkers.[21)]

The study consisted of a screening period (up to 4 weeks), a treatment period (48 weeks), and a follow-up period (4 weeks[35)]).

Subjects orally received placebo or aceneuramic acid 2 g three times daily after meals, with the recommended dosing interval of approximately 8 hours.

All of 89 randomized subjects (44 in the placebo group, 45 in the aceneuramic acid group) were included in the safety analysis set. Of these, 88 subjects (43 in the placebo group, 45 in the aceneuramic acid group) were included in the population for efficacy analysis, and the remaining 1 subject in the placebo group was excluded because the subject discontinued the study due to non-attendance after the visit prior to the start of study drug. Among the randomized subjects, 2

31) The study was conducted in the US, Italy, France, Canada, the UK, Bulgaria, and Israel.
32) Based on the results of the foreign phase II study, it was determined that approximately 80 subjects would need to be randomized, assuming a between-group difference in the primary endpoint "the change from baseline in total upper limb muscle strength" to be approximately 5 kg, with a SD of 6 kg, and a t-test (two-sided significance level of 5%) providing 90% power.
33) Randomization was stratified by gender, ensuring the proportion of either gender not greater than 60%.
34) The difference between 2 measurements of muscle strength in the subject's dominant hand was less than 15%.
35) As a rule, the follow-up period was omitted in subjects who entered the foreign long-term treatment study (Reference CTD 5.3.5.2-4, Study UX001-CL302 [Reference CTD 5.3.5.2-4] ["Study CL302"]).

subjects discontinued the study (1 in the placebo group due to non-attendance, 1 in the aceneuramic acid group due to poor medication compliance).

Table 28 shows the change from baseline in total upper limb muscle strength score[17)18)] at Week 48, the primary endpoint. There was no statistically significant difference between the placebo group and the aceneuramic acid group.

Table 28. Change from baseline in total upper limb muscle strength score at Week 48 (efficacy analysis set)

Treatment	Baseline	Week 48	Change from baseline[a) b)]	Between-group difference in change[b)] [95% CI]	*P* value
Placebo	56.31 ± 29.29 (43)	53.03 ± 28.75 (43)	−2.99 ± 0.87		
Aceneuramic acid	55.99 ± 26.95 (45)	53.54 ± 29.09 (44)	−2.25 ± 0.77	0.74 [−1.61, 3.09]	0.5387

Unit, kg; mean ± SD (number of subjects evaluated)
To calculate the total muscle strength score, (1) if the muscle strength could not be measured due to severe muscle weakness, a score of 0 was given; (2) if the muscle strength on neither side could be measured for other reasons (such as pain, injury, or contracture), the missing value was not replaced; and (3) if the muscle strength could not be measured only on one side, the missing value was replaced with the value obtained on the opposite side.
a) Least squares mean ± SE
b) Calculated by a GEE model of compound symmetric covariance structure using change from baseline as the dependent variable; treatment group, time point (Week 8, 16, 24, 32, 40, and 48), and the interaction term between treatment group and time point as fixed effects; and baseline value, sex, and region as covariates.

Table 29 shows the proportion of subjects with any adverse event and the incidence of adverse events reported in ≥5% of subjects in either group.

Table 29. Proportion of subjects with any adverse event and incidence of adverse events reported in ≥ 5% of subjects in either group (safety analysis set)

	Placebo	Aceneuramic acid
N	44	45
Any adverse event	36 (81.8)	43 (95.6)
Adverse events reported in ≥5% of subjects in either group		
Abdominal pain upper	3 (6.8)	10 (22.2)
Arthralgia	5 (11.4)	9 (20.0)
Diarrhoea	6 (13.6)	8 (17.8)
Fall	7 (15.9)	7 (15.6)
Headache	7 (15.9)	7 (15.6)
Flatulence	5 (11.4)	6 (13.3)
Muscular weakness	3 (6.8)	6 (13.3)
Myalgia	1 (2.3)	6 (13.3)
Back pain	4 (9.1)	5 (11.1)
Cough	4 (9.1)	5 (11.1)
Nausea	2 (4.5)	5 (11.1)
Upper respiratory tract infection	1 (2.3)	5 (11.1)
Influenza like illness	11 (25.0)	4 (8.9)
Abdominal distension	4 (9.1)	4 (8.9)
Fatigue	4 (9.1)	4 (8.9)
Pain in extremity	3 (6.8)	4 (8.9)
ATP increased	2 (4.5)	4 (8.9)
Musculoskeletal pain	2 (4.5)	4 (8.9)
Oropharyngeal pain	2 (4.5)	4 (8.9)
Nasal congestion	1 (2.3)	4 (8.9)
Contusion	0	4 (8.9)
Dizziness	1 (2.3)	3 (6.7)
Dysgeusia	0	3 (6.7)
Frequent bowel movements	0	3 (6.7)
Gastritis	0	3 (6.7)
Taste disorder	0	3 (6.7)
Asthenia	3 (6.8)	2 (4.4)
Influenza	4 (9.1)	1 (2.2)
Pain	3 (6.8)	1 (2.2)
Sleep disorder	4 (9.1)	0
Sciatica	3 (6.8)	0
Skin abrasion	3 (6.8)	0

n (%)

No death occurred. Serious adverse events other than death were reported in 2.3% (1 of 44) of subjects in the placebo group (abortion [reported as voluntary abortion]) and in 4.4% (2 of 45) of subjects in the aceneuramic acid group (acute myocardial infarction in 1 subject and gastritis in 1 subject). A causal relationship to the study drug could not be ruled out for the adverse events reported in the aceneuramic acid group. There were no adverse events leading to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Appropriateness of the study design and the efficacy evaluation policy for aceneuramic acid

7.R.1.1 Efficacy endpoints in the Japanese phase III studies

PMDA asked the applicant to explain the rationale for setting the primary endpoint and other efficacy endpoints of the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1).

The applicant's explanation about the outcome measures used for the primary and secondary endpoints of the Japanese phase III studies:
DMRV is a disease characterized by a gradual progression of muscle weakness due to the atrophy of muscle tissue and degeneration of muscle fibers primarily in the distal muscles. The degree of progression of muscle weakness is known to vary significantly among individuals. Additionally, lower limb muscle strength is impaired earlier than upper limb muscle strength in patients with DMRV, and progressive muscle weakness in their lower legs will lead to walking difficulty. Concurrently, upper limb muscle weakness begins in the fingers and gradually extends to the entire upper limb, eventually necessitating assistance. Considering the progression of muscle weakness in DMRV and the rarity of the disease, the applicant decided to focus on upper limb muscle strength to evaluate the efficacy of aceneuramic acid. This decision allows patients to participate in the clinical study regardless of the degree of lower limb muscle weakness and permits the assessment of the drug's effect in slowing the decline of remaining muscle strength. The results from a foreign phase I study (Reference CTD 5.3.5.4-1, Study UX001-CL102 [Reference CTD 5.3.5.4-1] ["Study CL102"])[36] conducted to evaluate the efficacy of aceneuramic acid in patients with DMRV indicated that muscle strengths were evaluable using the following: Grip strength (forearm muscle group and intrinsic hand muscles), which represents muscle strengths in severely affected muscles in patients with DMRV, and muscle strengths in each of the shoulder abductor (deltoid), elbow flexor (biceps brachii), and elbow extensor (triceps brachii), which are the proximal muscles commonly affected by muscle diseases. Subsequently, the foreign phase II study (Study CL201) employed the total upper limb muscle strength score, which is the sum of the 4 muscle strengths. The change from baseline in the total upper limb muscle strength score suggested the efficacy of aceneuramic acid versus placebo [see Section 7.2.1]. Based on these findings and on the total upper limb muscle strength score chosen as the primary endpoint in the foreign phase III study, the Japanese phase III studies also used the total upper limb muscle strength score as the primary endpoint. Furthermore, the secondary endpoints of the Japanese phase III studies included the upper limb scores[29] from the GNEM-FAS,[28] which was developed to assess the impact of muscle strength changes on functional status in patients with DMRV. These efficacy endpoints were used to evaluate the efficacy of aceneuramic acid in suppressing muscle weakness in DMRV.

The applicant's explanation about the rationale for choosing Week 48 for the primary endpoint of the Japanese phase III studies:
In the foreign phase II study, the efficacy endpoint of "change from baseline in total upper limb muscle strength at Week 24" suggested a tendency toward suppressed progression of muscle weakness in the aceneuramic acid 2 g group compared to the placebo group. The change from baseline in total upper limb muscle strength at Week 48 indicated a stronger tendency toward suppressed progression of muscle weakness in the aceneuramic acid 2 g group compared to the aceneuramic acid 1 g group [see Section 7.2.1]. Based on the above results, Week 48 was chosen for the primary endpoint in the foreign phase III study. For the above reasons, the Japanese phase III studies also selected Week 48 for the primary endpoint.

[36] In the foreign phase I study (Study CL101), 12 of 26 enrolled subjects were evaluated for muscular strength using dynamometer-based muscle strength measurements (knee, hip, upper limbs), a 6-minute walk test, a gait speed test, and a sit-to-stand test.

In summary, the primary endpoint employed in the Japanese phase III studies was the change from baseline in the total upper limb muscle strength score at Week 48.

PMDA's view:
Considering the progression of muscle weakness in DMRV and the rarity of the disease, the applicant selected the primary endpoint in Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1) which allows as many patients as possible to participate in the studies, regardless of the degree of lower limb muscle weakness, and which enables evaluation of the effect of aceneuramic acid in slowing the decline of remaining muscle strength. The applicant's approach is understandable. Further, in view of the changes over time in upper limb muscle strength scores in the foreign phase II study (Study CL201), the applicant decided to evaluate the change from baseline in total upper limb muscle strength scores as the primary endpoint variable at Week 48. The applicant's decision is reasonable. However, since it is also important to use a measure that focuses on the impact of muscle strength changes on the activities of daily living of patients with DMRV, the efficacy of aceneuramic acid should be evaluated based on the primary endpoint of total upper limb muscle strength score, along with the secondary endpoint of the GNEM-FAS upper limb scores.

7.R.1.2 Efficacy evaluation policy for aceneuramic acid

PMDA asked the applicant to explain the development history and efficacy evaluation policy for aceneuramic acid in Japan.

The applicant's explanation:
After the Japanese phase I study (1) (Sialic Acid-1 study) using the immediate-release tablet of aceneuramic acid, which was the first-in-human clinical study, the overseas development company Ultragenyx (the US) conducted a foreign phase I study (Study CL101) using Acenobel, i.e., the extended-release tablet of aceneuramic acid. The results of the study showed an increase in free aceneuramic acid concentration in patients with DMRV [see Section 6.2.2.2] without any significant safety concerns identified, leading to the conduct of the foreign phase II study (Study CL201). In Study CL201, the change from baseline in the total upper limb muscle strength score at Week 24, the primary efficacy endpoint, indicated a trend toward suppressed progression of muscle weakness in the aceneuramic acid 2 g group compared to the placebo and aceneuramic acid 1 g groups [see Section 7.2.1]. Accordingly, the foreign phase III study (Study CL301) was planned.

After the foreign phase II study, a Japanese phase I study (2) (Sialic Acid-2 study) using the extended-release tablet of aceneuramic acid was conducted in Japan. In light of inter-individual and intra-individual variability, there were no significant differences in the pharmacokinetics of aceneuramic acid between Japanese and non-Japanese patients [see Sections 6.2.2.2 and 6.2.2.3], and [redacted]. Therefore, a Japanese clinical study was planned for the development of aceneuramic acid in Japan. Because of the extremely limited number of patients with DMRV, it was infeasible to perform statistical hypothesis testing between the placebo and aceneuramic acid groups in the Japanese phase III study (1) (Sialic Acid-3 study). Thus, the applicant planned to evaluate the efficacy of aceneuramic acid in Japanese patients with DMRV,

based on not only the results of the Japanese phase III study (1)but also the results of the simultaneously conducted foreign phase III study.

The change from baseline in upper limb muscle strength scores at Week 48, the primary endpoint, in the foreign phase III study suggested a trend toward suppressed progression of muscle weakness in the aceneuramic acid group compared to the placebo group. However, no statistically significant difference was observed between the aceneuramic acid and placebo groups [see Section 7.3.4]. Additionally, the point estimate for the change from baseline in GNEM-FAS upper limb score at Week 48, a secondary endpoint, did not indicate a trend toward a suppressed decline in the score in the aceneuramic acid group compared to the placebo group. Thus, an additional Japanese phase III study (2) (Study NPC-09-1) was planned to confirm the efficacy of aceneuramic acid. In the Japanese phase III study (2), as in the preceding Japanese phase III study (1), statistical hypothesis testing between the placebo and aceneuramic acid groups was not planned for the same reasons, and the sample size was determined from the perspective of feasibility. The efficacy of aceneuramic acid in Japanese patients with DMRV was comprehensively evaluated based on the results of the 2 Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1).

PMDA asked the applicant to explain the rationale for evaluating the efficacy of aceneuramic acid based on the results of the 2 Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), taking into account the factors that precluded the testing of hypothesis on the efficacy of aceneuramic acid in the foreign phase III study.

The applicant’s explanation:
When the results of the foreign phase III study became available, a comparison of the baseline characteristics of subjects from the foreign phase II study, the Japanese phase III study (1), and the foreign phase III study revealed that while subject characteristics were generally similar in the foreign phase II study and the Japanese phase III study (1), the foreign phase III study exhibited notable differences from other studies. Specifically, the median disease duration was shorter and the median baseline total upper limb muscle strength score was higher in the foreign phase III study than in the foreign phase II study and the Japanese phase III study (1). In addition, the distributions of disease duration and baseline total upper limb muscle strength scores were broader in the foreign phase III study. These factors suggest greater inter-individual variability in the rate of upper limb muscle strength decline in the foreign phase III study than in the foreign phase II study and the Japanese phase III study (1). A post-hoc analysis was conducted to explore the possibility that subjects enrolled in the foreign phase III study were not selected based on a predicted progression of muscle weakness during the study period. This efficacy analysis focused on a subgroup with “a baseline GNEM-FAS upper limb score of ≥30” and “disease duration of ≥5 and ≤15 years,” where a decline in upper limb muscle strength within the study period (48 weeks) was anticipated with a certain degree of muscle strength remaining. The results indicated a trend toward slower progression of upper limb muscle weakness in the aceneuramic acid group than in the placebo group, and a similar trend was observed in the foreign phase II study and the Japanese phase III study (1). The efficacy of aceneuramic acid might not have been demonstrated in the foreign phase III study due to the inclusion of diverse subjects from 7 countries and the lack of appropriate patient population selection for evaluating the efficacy of

aceneuramic acid. In addition, limiting the patient population to those with a baseline GNEM-FAS upper limb score of ≥30 would restrict the number of eligible patients. Given these considerations, the Japanese phase III study (2), an efficacy-confirmatory study, was designed to include patients with "baseline GNEM-FAS upper limb score of ≥24" and "disease duration of ≥5 and ≤15 years," so as to more appropriately assess the efficacy of aceneuramic acid.

Based on the above considerations, the results from the 2 Japanese phase III studies can be used to evaluate the efficacy of aceneuramic acid in Japanese patients with DMRV.

PMDA's view:
The foreign phase III study (Study CL301) could not demonstrate the superiority of aceneuramic acid over placebo in the primary endpoint. Although there are limitations to the interpretation of data from the limited number of subjects in both Japanese and foreign clinical studies, it is somewhat understandable that the applicant attributed the lack of demonstrated efficacy in the foreign phase III study to the inclusion of a patient population with more diverse characteristics compared to those in the foreign phase II study (Study CL201) and the Japanese phase III study (1) (Sialic Acid-3 study). It is also understandable that, given the feasibility of the study, the applicant decided to conduct an additional clinical study by modifying the inclusion criteria to enroll patients who are more suitable for assessing the efficacy of aceneuramic acid, for the more appropriate evaluation of its efficacy. DMRV is an extremely rare disease with a prevalence of 1 in 1,000,000 worldwide, with higher prevalence in the Middle East (including Israel) and Japan than in other regions (*J Neurol Neurosurg Psychiatry.* 2015;86:385-92). There are an estimated number of 1,000 to 2,000 patients globally, and 167 to 345 patients in Japan (2009 Report, Estimated number of patients with each type of distal myopathy in Japan and DMRV genetic diagnosis [in Japanese], funded by Health and Labour Sciences Research Grant [Research Project on Intractable Diseases]). There are no approved drugs for DMRV in or outside of Japan. Considering these points, PMDA will focus on the results of the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1) and comprehensively evaluate the efficacy of aceneuramic acid, although the studies included no planned statistical hypothesis test.

7.R.2 Efficacy

The applicant's explanation about the efficacy of aceneuramic acid:
In the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), a between-group comparison based on point estimates was conducted to assess the change from baseline in the total upper limb muscle strength score at Week 48, the primary endpoint. The results indicated a trend toward a suppressed decline in upper limb muscle strength in the aceneuramic acid group compared to the placebo group in both studies (Tables 22 and 24). The changes over time in the total upper limb muscle strength score from baseline for individual subjects in each study are illustrated in Figures 1 and 2. In both studies, while the scores of subjects in the placebo group generally tended to be maintained or worsened from baseline throughout the evaluation period, a certain number of subjects in the aceneuramic acid group had an improved or maintained score from baseline throughout the evaluation period.

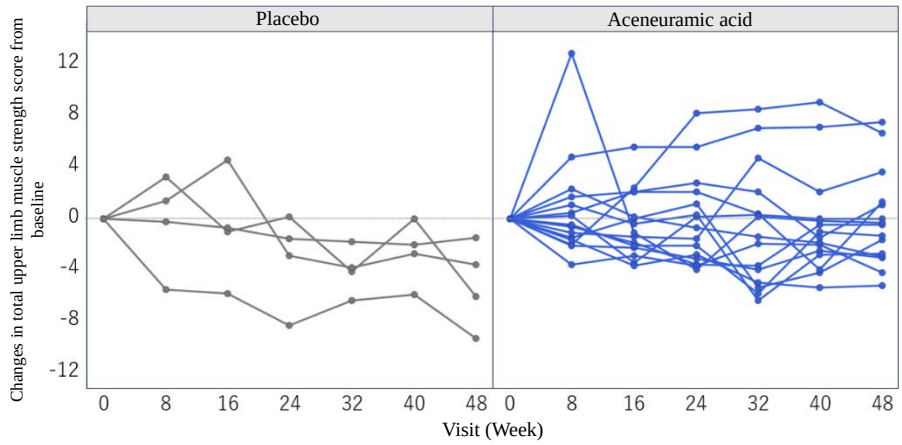

Figure 1. Changes over time in the total upper limb muscle strength score from baseline in Japanese phase III study (1)

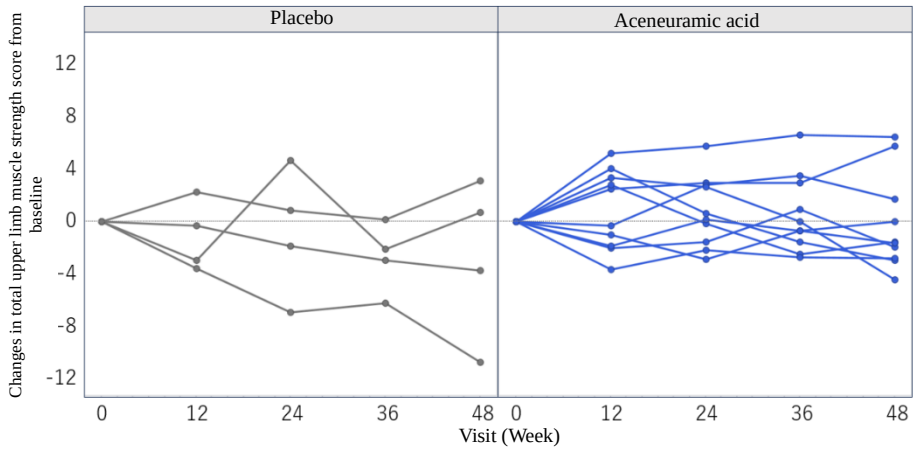

Figure 2. Changes over time in the total upper limb muscle strength score from baseline in Japanese phase III study (2)

Table 30 shows the change from baseline in the GNEM-FAS[28] upper limb score[29] at Week 48, the secondary endpoint, in the Japanese phase III studies. In both studies, there was a trend toward a suppressed decline in the score in the aceneuramic acid group compared to the placebo group.

Table 30. Changes from baseline in GNEM-FAS upper limb score in Japanese phase III studies

Study	Treatment	N	Baseline	Week 48	Change [95% CI]
Japanese phase III study (1)	Placebo	4	28.8 ± 5.3 31.0 (21, 32)	28.0 ± 6.7 31.0 (18, 32)	−0.8 ± 1.7 [−3.5, 2.0]
	Aceneuramic acid	15	25.9 ± 7.1 29.0 (5, 32)	26.8 ± 5.6 29.0 (13, 32)	0.9 ± 2.8 [−0.7, 2.4]
Japanese phase III study (2)	Placebo	4	28.0 ± 2.2 27.5 (26, 31)	25.5 ± 2.4 24.5 (24, 29)	−2.5± 0.6 [−3.4, −1.6]
	Aceneuramic acid	10	27.4 ± 2.8 26.5 (24, 32)	26.5 ± 3.7 27.0 (21, 32)	−0.9 ± 2.0 [−2.3, 0.5]

Upper row, Mean ± SD; Lower row, Median (min., max.)

The studies yielded consistent results for the efficacy of aceneuramic acid in the suppression of the progression of muscle weakness in Japanese patients with DMRV.

PMDA's view:
The point estimates of the change from baseline in the total upper limb muscle strength score at Week 48, the primary endpoint of the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), indicated a trend toward suppressed progression of muscle weakness in the aceneuramic acid group compared to the placebo group in both studies. In addition, the review of the changes over time in the total upper limb muscle strength score from baseline for individual subjects suggested that a certain number of subjects in the aceneuramic acid group had an improved or maintained score. The results on the change from baseline in GNEM-FAS upper limb score at Week 48 also showed a trend toward a suppressed decline in the score in the aceneuramic acid group compared to the placebo group.

Based on the above results of the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), aceneuramic acid exhibits certain efficacy in suppressing the progression of muscle weakness in patients with DMRV.

Considering that DMRV for which aceneuramic acid is indicated is a rare and serious disease with no existing treatments in or outside of Japan, and given the high medical need for therapies for DMRV, the results of efficacy evaluation in the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1) support the significance of making aceneuramic acid available for use in clinical practice in Japan.

7.R.3 Safety

PMDA's view:
In review of the discussion in Sections 7.R.3.1 and 7.R.3.2 based on the clinical study results submitted, attention should be paid to the risk of adverse events related to hepatic dysfunction in patients treated with aceneuramic acid, but other events reported in clinical studies are unlikely to be major problems associated with the use of aceneuramic acid in clinical practice. Based on the above, the safety of aceneuramic acid in Japanese patients with DMRV is acceptable.

7.R.3.1 Adverse events reported in clinical studies

PMDA asked the applicant to explain the safety of aceneuramic acid based on the results of Japanese phase III studies including long-term treatment study (Sialic Acid-3 study, Study NPC-09-1, Sialic Acid-4 study) and the foreign phase III study (Study CL301).

The applicant's explanation:
The incidences of adverse events in the phase III placebo-controlled studies (Sialic Acid-3 study, Study NPC-09-1, and Study CL301) were assessed (Tables 23, 25, and 29, respectively). No death occurred in any of the studies. In the Japanese phase III study (1) (Sialic Acid-3 study), a serious adverse event for which a causal relationship to the study drug could not be ruled out occurred in 1 subject (foetal death) in the aceneuramic acid group. Aceneuramic acid was administered to the subject for 15 days during the first month of pregnancy and then discontinued, with the fetus developing well for about 3 months of pregnancy. For this and other reasons, the investigator

considered that the causality with the study drug was low but could not be completely ruled out.[37] In the foreign phase III study, serious adverse events for which a causal relationship to the study could not be ruled out were reported in 2 subjects (acute gastritis and acute myocardial infarction in 1 subject each) in the aceneuramic acid group, and the acute gastritis resolved. The acute myocardial infarction occurred during treatment with aceneuramic acid in a subject with a history of hypertension, etc. Percutaneous coronary intervention was performed, and the patient recovered. The administration of aceneuramic acid was continued after the event, with no recurrence of myocardial infarction. The investigator considered that the causality with the study drug was low but could not be completely ruled out.[38] In the Japanese phase III study (2) (Study NPC-09-1), there were no serious adverse events for which a causal relationship to the study drug could not be ruled out. Furthermore, no adverse events leading to discontinuation of the study drug were reported in any of the studies.

In the phase III placebo-controlled clinical studies, adverse events related to gastrointestinal disorders such as abdominal pain upper, diarrhoea, and flatulence were relatively common. Although these events tended to occur more frequently in the aceneuramic acid group than in the placebo group, most events were mild to moderate. Events such as arthralgia, fall, muscular weakness, and myalgia, which are observed in patients with DMRV in general, were relatively common, but these events did not tend to occur more frequently in the aceneuramic acid group than in the placebo group.

Results of an analysis on the long-term safety of aceneuramic acid showed no trend toward an increase in the incidence of adverse events in the Japanese long-term treatment study (Table 27).

PMDA's view:
The adverse events reported in both Japanese and foreign clinical studies of aceneuramic acid, based on the applicant's explanation, are unlikely to pose significant problems for its clinical use. However, the relatively high incidence of hepatic dysfunction-related adverse events reported in foreign clinical studies will be further discussed in Section 7.R.3.2.

7.R.3.2 Adverse events related to hepatic dysfunction

PMDA asked the applicant to explain hepatic dysfunction-related adverse events associated with the use of aceneuramic acid.

The applicant's explanation:
In the Japanese phase III study (1) (Sialic Acid-3 study), hepatic function abnormal was reported in 1 subject in the aceneuramic acid group. The causal relationship to the study drug could not be ruled out, and the event was moderate and not serious. The adverse event resolved while the administration of the study drug was continued. In the Japanese phase III study (2) (Study NPC-09-1), hepatic dysfunction was reported in 1 subject in the aceneuramic acid group. The event was mild and not

[37] A woman in her 30s underwent urine pregnancy tests at the screening for study participation and before administration of the study drug, and her negative test results led to the initiation of the study drug. However, due to a delayed menstrual cycle, the subject decided to discontinue the study drug on Day 15. On Day 16, a pregnancy test was positive, and the result was reported to the investigator, leading to the termination of the study. Although the fetus initially developed well, no fetal heartbeat was detected in the fifth month of pregnancy, with a diagnosis of fetal death. The mother's health remained unaffected.

[38] A man in his 40s, a smoker with comorbidities including hypertension, dyslipidemia, hypertriglyceridemia, and elevated liver enzymes, was concomitantly taking antihypertensive drugs, cholesterol synthesis inhibitors, and acetylsalicylic acid. On Day 51, the patient was hospitalized, underwent percutaneous coronary intervention, recovered, and was discharged on the following day.

serious, and the causal relationship to the study drug was ruled out. In the foreign phase III study (Study CL301), hepatic dysfunction-related adverse events were reported in 3 subjects in the placebo group (alanine aminotransferase [ALT] increased in 2 subjects, liver function test increased in 1 subject) and in 4 subjects in the aceneuramic acid group (ALT increased in 4 subjects). A causal relationship to the study drug could not be ruled out for any of the events observed in the aceneuramic acid group, but these events were mild to moderate in severity and not serious. The events resolved while the administration of the study drug was continued.

Additionally, in other foreign clinical studies of aceneuramic acid, hepatic dysfunction-related adverse events leading to discontinuation of the study drug were reported in 2 subjects (hepatic enzyme abnormal in 1 subject[39] and ALT increased/aspartate aminotransferase [AST] increased in 1 subject[40]) in the aceneuramic acid group. The hepatic enzyme abnormal was mild in severity, while the ALT increased and AST increased were moderate and severe, respectively. Given this, these adverse events are unlikely to pose significant clinical problems because all the events resolved, with no serious adverse events reported, although the risk of hepatic dysfunction-related adverse events such as liver function test abnormal cannot be ruled out.

PMDA's view:
Given the hepatic dysfunction-related adverse events reported in Japanese and foreign clinical studies, including events for which a causal relationship to aceneuramic acid cannot be ruled out and severe events leading to treatment discontinuation, attention should be paid to the possible risk of hepatic dysfunction-related events in patients treated with aceneuramic acid.

7.R.4 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication of aceneuramic acid.

The applicant's explanation:
The Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1) have demonstrated a certain level of efficacy of aceneuramic acid in slowing the progression of muscle weakness in patients with DMRV [see Section 7.R.2]. Aceneuramic acid is expected to normalize hyposialylation in muscle tissues of patients with DMRV and to slow the progression of muscle weakness by suppressing the atrophy and fibrosis of muscle tissues [see Section 3.R.1]. This mechanism suggests that aceneuramic acid can suppress the progression of muscle weakness regardless of muscle location such as the muscles of the upper limb, as long as some muscle strength remains. Therefore, "Suppression of the progression of muscular weakness in patients with GNE myopathy" was selected as the indication. At the time of submission of the present application, the proposed indication was "GNE myopathy." However, considering that the disease name used for designated intractable diseases in Japan is "distal myopathy with rimmed vacuoles (DMRV)," the indication was revised as follows:

[39] Event reported in the aceneuramic acid 1 g group of the foreign phase II study (Study CL201).
[40] Event reported in the foreign long-term treatment study (Reference CTD 5.3.5.2-4, Study CL302).

Revised proposed indication (draft)
Suppression of the progression of muscular weakness in patients with distal myopathy with rimmed vacuoles

PMDA asked the applicant to explain the necessity of limiting the use of aceneuramic acid to patients with DMRV with mutations in the *GNE* gene.

The applicant's explanation:
The Japanese and foreign clinical studies of aceneuramic acid included patients with DMRV with mutations in the *GNE* gene who met the diagnostic criteria for "Definite" DMRV (https://www.nanbyou.or.jp/entry/4003, last accessed on January 25, 2024). However, according to the diagnostic criteria for DMRV, patients who have no confirmed mutation in the *GNE* gene but meet the criteria for both clinical features and muscle biopsy findings are also diagnosed as DMRV (classified as "Probable"). When patients with a diagnosis of DMRV undergo testing for *GNE* gene variants, some patients may have a negative test result for mutations due to detection sensitivity or other factors. Given the above situations, the use of aceneuramic acid should not be limited only to patients with confirmed mutations in the *GNE* gene because aceneuramic acid could be effective not only in patients with "Definite" DMRV but also in those with "Probable" DMRV.

PMDA's view:
In view of the results of the Japanese phase III study (Sialic Acid-3 study and Study NPC-09-1) and the pharmacological actions of aceneuramic acid, the indication should be "suppression of the progression of muscular weakness in patients with distal myopathy with rimmed vacuoles." Considering the development concept of aceneuramic acid [see Sections 3.R.1 and 6.R.1], the presence of mutations in the *GNE* gene should be confirmed before determining the eligibility of patients for treatment with aceneuramic acid. However, considering the applicant's explanation, a false-negative genetic test result may result in lost treatment opportunities for patients with no other existing treatment options, which is undesirable. To avoid this consequence, it is acceptable not to limit the use of aceneuramic acid only to patients with confirmed mutations in the *GNE* gene.

7.R.5 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration of aceneuramic acid.

The applicant's explanation:
(a) Dosing regimen
According to an assessment of the pharmacokinetics of serum free aceneuramic acid in the foreign phase I study (Study CL101) investigating the effects of food intake, AUC increased and t_{max} was delayed following the administration of aceneuramic acid under postprandial conditions, compared to that under fasting conditions [see Section 6.1.1]. Based on these findings, aceneuramic acid was administered orally three times daily after meals.

(b) Dose level of aceneuramic acid determined in the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1)

In the foreign phase II study, the change from baseline in total upper limb muscle strength score at Week 24 showed a decreasing trend in both the placebo group and the aceneuramic acid 1 g group, whereas an increasing trend was observed in the aceneuramic acid 2 g group [see Section 7.2.1]. In the extension study (Reference CTD 5.3.5.2-2, Study UX001-CL202 [CTD 5.3.5.2-2] ["Study CL202"]) of the foreign phase II study (Study CL201), an investigation was conducted to assess whether the four-times daily or three-times daily regimen (aceneuramic acid 12 g/day) of aceneuramic acid at 3 or 4 g (1.5 or 2 g in extended-release tablets, 1.5 or 2 g in immediate release capsules) provides greater efficacy compared to the three-times daily regimen of aceneuramic acid 2 g (aceneuramic acid 6 g/day). The results showed no difference in efficacy between the 6 g/day and 12 g/day dosages. However, the incidence of adverse events related to gastrointestinal disorders such as flatulence, diarrhoea, dyspepsia, and nausea tended to increase with the 12 g/day dosage compared to the 6 g/day dosage. Based on the above findings, oral administration of aceneuramic acid 2 g three times daily after meals was chosen as the dosage in the Japanese phase III study.

(c) Dosing interval

The dosing interval in the Japanese phase III studies was approximately 8 hours because the time during which aceneuramic acid supplemented by administration remains cleared from the serum should be minimized wherever possible.

Considering that the two Japanese phase III studies showed a tendency toward suppressed progression of muscle weakness in the aceneuramic acid group [see Section 7.R.2], and from the perspective of compliance in clinical practice, the dosage regimen of aceneuramic acid 2 g orally three times daily after meals should be selected, as in the Japanese phase III studies.

Initially, the proposed dosage regimen allowed dose adjustment according to the patient's condition. However, the aceneuramic acid 1 g group in the foreign phase II study (Study CL201) did not show the efficacy of the lower dose, and doses below 2 g per administration were not examined in the Japanese phase III studies. Thus, with no data available that show the efficacy of aceneuramic acid at <2 g in the submitted clinical study data, the option of reducing the dose from 2 g should be deleted.

PMDA's view:

Regarding the dosage regimen of aceneuramic acid in the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), aceneuramic acid 2 g should be administered orally three times daily after meals, in view of the differences in the pharmacokinetics of aceneuramic acid between the fasting and postprandial states, as well as the results of the foreign phase II study (Study CL201) investigating multiple dosage regimens. On the other hand, the necessity of specifying a dosing interval of approximately 8 hours in the Japanese phase III studies is uncertain, given the unclear pharmacokinetic parameters of serum free aceneuramic acid which is associated with the efficacy of aceneuramic acid. However, a certain level of efficacy and acceptable safety of aceneuramic acid were confirmed in the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1) under the prescribed dosage regimen [see Sections 7.R.2 and 7.R.3], and therefore, the dosage regimen of

aceneuramic acid (including dosing intervals) should be specified as defined by the protocols in these studies. The revised dosage regimen is shown below.

Revised dosage and administration (draft)
The usual adult dosage is 2 g of aceneuramic acid orally administered three times daily after meals, approximately 8 hours apart.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations for aceneuramic acid:
To assess the safety and efficacy of aceneuramic acid, the applicant plans to conduct a general use-results survey, covering all patients with DMRV who have been treated with aceneuramic acid in the post-marketing setting.

Since adverse events related to hepatic dysfunction, including severe cases, were reported in clinical studies of aceneuramic acid [see Section 7.R.3.2], hepatic dysfunction is identified as a safety specification. The survey will capture the occurrence of adverse events related to hepatic dysfunction (including liver function tests abnormal) in routine clinical practice, and evaluate the risk of these adverse events associated with the use of aceneuramic acid.

For efficacy evaluation, the applicant considered the feasibility of using external data such as patient registries as a comparator. However, identifying patients with the results of outcome measures such as grip strength was challenging, and the use of external data was considered impractical. Therefore, this survey plans to assess the efficacy of aceneuramic acid by evaluating data on variables that can be measured in routine clinical practice (such as grip strength and GNEM-FAS), and to compare the findings with the clinical study data obtained to date.

PMDA's view:
Given the limited number of patients treated with aceneuramic acid in the clinical studies conducted so far, the rarity of DMRV, and the submitted clinical study data, the occurrence of adverse events related to hepatic dysfunction in clinical practice should be monitored through the post-marketing surveillance covering all patients treated with aceneuramic acid, as proposed by the applicant. Furthermore, the efficacy of aceneuramic acid should be confirmed in this surveillance and the obtained information should be appropriately provided to healthcare professionals and patients.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that aceneuramic acid has efficacy in suppressing the progression of muscular weakness in patients with DMRV, and that aceneuramic acid has acceptable safety in view of its benefits. Aceneuramic acid is clinically meaningful because it offers a new therapeutic option for suppressing the progression of muscular weakness in patients with DMRV.

PMDA has concluded that aceneuramic acid may be approved if aceneuramic acid is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 21, 2024

Product Submitted for Approval

Brand Name	Acenobel Extended Release Tablets 500 mg
Non-proprietary Name	Aceneuramic Acid
Applicant	Nobelpharma Co., Ltd.
Date of Application	July 26, 2023

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the safety of aceneuramic acid and the dosage regimen described in the Review Report (1).

1.1 Efficacy

The expert advisors provided the following comments regarding the appropriateness of the study design, the efficacy evaluation policy, and the efficacy of aceneuramic acid and supported the PMDA's conclusions described in Sections "7.R.1 Evaluation of the appropriateness of the study design and the efficacy evaluation policy for aceneuramic acid" and "7.R.2 Efficacy" of the Review Report (1).

- In the foreign phase III study, which included statistical hypothesis testing, no significant difference was observed between the aceneuramic acid group and the placebo group for the primary endpoint (Table 28). The applicant's explanation that this may be due to the inclusion of a patient population with a broad spectrum of patient characteristics [see Section 7.R.1.2] is understandable. The Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1), however, showed a trend toward a suppressed decline of upper limb muscle strength for the primary endpoint (Tables 22 and 24). Taking feasibility into account, the inclusion criteria for an additional study were modified to include patients more suitable for accurately assessing the efficacy of aceneuramic acid. The resultant Japanese phase III study (2) (Study NPC-09-1) suggested the efficacy of aceneuramic acid, as shown in the changes over time in the total upper limb muscle strength score from baseline for individual subjects (Figure 2).

- Although no studies have demonstrated the superiority of aceneuramic acid over placebo, a consistent trend toward slowing the progression of upper limb muscle weakness in the aceneuramic acid group compared to the placebo group was observed in the foreign phase II study (Study CL201), the foreign phase III study (Study CL301), and the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1). Given DMRV defined as a rare disease and the development concept of aceneuramic acid [see Sections 3.R.1 and 6.R.1], it is reasonable to conclude that the efficacy of aceneuramic acid is sufficient for approval.
- Given the extreme rarity of DMRV and the significant individual variability in its pathological conditions, the applicant considered that statistical hypothesis testing-based efficacy evaluation in Japanese clinical studies was challenging. The applicant's decision is inevitable. Under the above limitations, the results of the Japanese phase III studies and other data that were submitted to support the efficacy of aceneuramic acid were evaluated in a comprehensive manner, based on inter-group comparison using point estimates of the total upper limb muscle strength score. The maximum interpretation of the results is that there was a trend toward a suppressed decline in the total upper limb muscle strength score, albeit no improvement was noted.
- Treatment to improve muscle weakness in DMRV is challenging, and a focus should therefore be placed on slowing the progression of the symptom first. Given that DMRV is a rare and serious disease with no available treatment options either in Japan or in foreign countries, and that there is a high medical need for a therapy for DMRV, the expert advisors have no objection to the PMDA's conclusion that it is of clinical significance to made aceneuramic acid available for use in clinical practice in Japan on the basis of the efficacy data from the Japanese phase III studies (Sialic Acid-3 study and Study NPC-09-1).
- In view of the results of Japanese and foreign clinical studies of aceneuramic acid, the efficacy of aceneuramic acid should be continually evaluated in the post-marketing setting and factors affecting the efficacy (patient characteristics, concomitant therapies, etc.) should be investigated.

Based on the above considerations, PMDA asked the applicant to include the following cautionary statement in the "Precautions Concerning Indication" section of the package insert: Aceneuramic acid should be used in patients considered to be eligible for treatment with aceneuramic acid by physicians with a full understanding of the information obtained in the Japanese and foreign clinical studies and the characteristics of patients included in the clinical studies, as well as the efficacy and safety of aceneuramic acid. PMDA also asked the applicant to provide detailed data from the Japanese and foreign clinical studies through materials and other means. The applicant has appropriately responded.

1.2 Indication

The indication proposed for aceneuramic acid was supported by the expert advisors. During the discussion on the appropriateness of use of aceneuramic acid in patient with DMRV regardless of the mutations in the *GNE* gene identified through the genetic testing, an expert advisor commented that aceneuramic acid should be used only in patients with mutations in the *GNE* gene confirmed by the genetic testing, in light of the subjects enrolled in the clinical studies. In contrast, the following comments were also raised from other expert advisors. At the end of the discussion, the PMDA's conclusion outlined in Section "7.R.4 Indication" of the Review Report (1) was supported by the expert advisors at the Expert Discussion.

- The notion that DMRV is a disease caused by mutations in the *GNE* gene is well established. However, current *GNE* genetic testing may not detect mutations in the *GNE* gene in cases of changes in the number of copies such as large-scale deletions and insertions, or large-scale significant genomic structural changes. The genetic test cannot necessarily identify *GNE* gene mutations in all patients with DMRV. In cases where family history is clear, genetic testing for *GNE* mutations may not be essential for diagnosing DMRV. The PMDA's conclusion that the use of aceneuramic acid is not restricted to patients with mutations in the *GNE* gene confirmed by genetic testing is appropriate.
- Considering the possibility that there may be a certain number of patients with DMRV in whom mutations in the *GNE* gene cannot be detected, such a situation that treatment opportunities may be lost in patients with no other existing treatment options should be avoided.

1.3 Risk management plan (draft)

The PMDA's conclusions described in Section "7.R.6 Post-marketing investigations" of the Review Report (1) were supported by the expert advisors at the Expert Discussion. PMDA has concluded that the current risk management plan (draft) for aceneuramic acid should include the safety specification presented in Table 31, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 32, and a use-results survey presented in Table 33.

Table 31. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
Not applicable	• Hepatic dysfunction	Not applicable
Efficacy specification		
• Efficacy of aceneuramic acid in patients with distal myopathy with rimmed vacuoles in clinical practice		

Table 32. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	• Use-results survey	• Disseminate data gathered during early post-marketing phase vigilance

Table 33. Outline of use-results survey (draft)

Objective	To investigate the safety and efficacy of aceneuramic acid in clinical practice
Survey method	All-case surveillance
Population	All patients with distal myopathy with rimmed vacuoles treated with aceneuramic acid
Observation period	120 weeks
Planned sample size	170 patients
Main survey items	Patient characteristics (disease duration, upper limb muscle strength, *GNE* genetic testing, muscle biopsy, etc.) Status of use of concomitant drugs and therapies Status of use of aceneuramic acid Efficacy-related parameters (grip strength, total upper limb muscle strength score, GNEM-FAS, etc.) Laboratory data (liver function test, etc.) Adverse events

1.4 Quality of the drug substance and the drug product

The applicant's explanation about the history of changes to the manufacturing process parameters during the blending/granulation/drying of the drug product:

Brown-colored substance was observed during granulation of 2 batches of the drug product manufactured at the commercial scale. To address this issue, the granulation process parameters were

adjusted to prevent the occurrence of brown-colored substance. No brown-colored substance was observed in the subsequent batches manufactured with the revised parameters.

Based on these production experiences, the granulation process parameters are modified to establish a more robust process.

PMDA's view:
The rationale behind the applicant's proposed changes to the granulation process parameters for a more robust manufacturing process is understandable to a certain extent. Regardless of the brown-colored substance, the dissolution behavior of the formulation manufactured under the revised granulation process parameters has not yet been confirmed to be equivalent to that used in clinical studies.

Based on the above, PMDA instructed the applicant to perform the following activities for at least 3 initial batches of the drug product manufactured under the revised granulation process parameters, before marketing each batch: To evaluate the adequacy of the manufacturing process after the process parameter change and to confirm that the dissolution behavior for the batches is equivalent to that of the clinical study formulation when tested under the conditions of the dissolution test conducted during the development phase. The applicant agreed to comply with this requirement.

PMDA's view on the information to be described in the Review Report (2) [see Sections 2.R.2 and 2.R.3]:
Based on the results of the photostability testing, the drug product is considered to be photo-stable. From the results of the validation of analytical procedure for acetic acid specified in the purity test of the drug substance (related substances), the established testing method is considered appropriate.

PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled, in view of the above assessments and the discussions in the Review Report (1).

1.5 Others

For the present application, the applicant had not conducted the necessary quality and toxicity studies and assessments, which should have been conducted by themselves prior to the regulatory submission. Consequently, data from these studies and assessments were not included in the application documents, resulting in substantial time and efforts required for the confirmation of the quality and toxicity during the review process. Furthermore, the assessments necessary for the pharmaceutical compliance assessment (GMP compliance inspection) were not conducted, requiring considerable time and efforts to check for the presence of these data during the inspection. PMDA considers that, for future pharmaceutical development, the applicant should establish procedures and internal systems to ensure that necessary quality and toxicity assessments are appropriately conducted prior to the regulatory submission.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Since the product is an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or as a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Suppression of the progression of muscular weakness in patients with distal myopathy with rimmed vacuoles

Dosage and Administration

The usual adult dosage is 2 g of aceneuramic acid orally administered three times daily after meals, approximately 8 hours apart.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered, to understand the characteristics of patients using the product. The applicant is also required to promptly collect data on the safety and efficacy of the product so that necessary measures are taken to ensure the proper use of the product.

Appendix

List of Abbreviations

Aceneuramic acid	Aceneuramic acid
Acenobel	Acenobel Extended Release Tablets 500 mg
ALT	Alanine aminotransferase
AMED	Japan Agency for Medical Research and Development
AST	Aspartate aminotransferase
AUC	Area Under Concentration-time Curve
BCRP	Breast cancer resistance protein
CL	Clearance
CQA	Critical quality attribute
CTD	Common Technical Document
DMRV	Distal myopathy with rimmed vacuoles
ESI-MS	Electrospray ionization-mass spectrometry
FAS	Full Analysis Set
GC	Gas chromatography
GNE/MNK	UDP-N-acetylglucosamine 2-epimerase/N -acetylmannosamine kinase
GNEM-FAS	GNE myopathy Functional Activities Scale
HEK293 cells	Human embryonic kidney 293 cells
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
ICH Q1B Guideline	“Stability Testing: Photostability Testing of New Drug Substances and Products” (PAB/ELD Notification No. 422 dated May 28, 1997)
ICH Q2B Guideline	“Validation of Analytical Procedures: Methodology” (PMSB/ELD Notification No. 338 dated October 28, 1997)
ICH Q3A Guideline	“Partial revision on ‘Revision of the Guidelines on Impurities in New Drug Substances’” (PFSB/ELD Notification No. 1204001 dated December 4, 2006)”
ICH Q3B Guideline	“Revision on ‘Revision of the Guidelines on Impurities in New Drug Products’” (PFSB/ELD Notification No. 0703004 dated July 3, 2006)”
IR	Infrared absorption spectroscopy
JST	Japan Science and Technology Agency
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LOCF	Last Observation Carried Forward
ManNAc	N-acetylmannosamine
MATE	Multidrug and Toxin Extrusion
mRNA	messenger Ribonucleic Acid
NEDO	New Energy and Industrial Technology Development Organization
NMR	Nuclear magnetic resonance spectroscopy
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
(Q)SAR	(Quantitative) Structure-Activity Relationship
QTc	Corrected QT
QTcF interval	Fridericia-corrected QT Interval
RH	Relative Humidity
Study CL101	Study UX001-CL101 (CTD 5.3.3.2-3)
Study CL102	Study UX001-CL102 (Reference CTD 5.3.5.4-1)
Study CL201	Study UX001-CL201 (CTD 5.3.5.1-3)
Study CL202	Study UX001-CL202 (CTD 5.3.5.2-2)
Study CL301	Study UX001- CL301 (Reference CTD 5.3.5.1-4)

Study CL302	Study UX001- CL302 (Reference CTD 5.3.5.2-4)
$t_{1/2}$	Elimination Half-Life
t_{max}	Time to Reach Maximum Concentration
UV/VIS	Ultraviolet-visible spectroscopy
Vd	Volume of distribution