Report on the Deliberation Results

March 7, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Beyonttra Tablets 400 mg
Non-proprietary Name	Acoramidis Hydrochloride (JAN*)
Applicant	Alexion Pharma GK
Date of Application	April 17, 2024

Results of Deliberation

In its meeting held on March 6, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

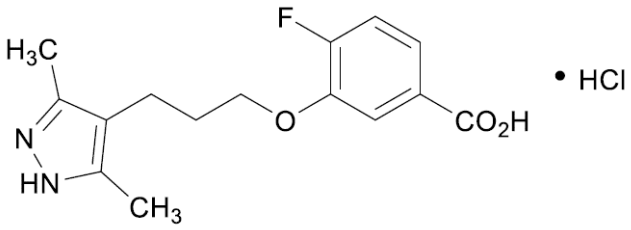
Review Report

February 13, 2025
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	Beyonttra Tablets 400 mg
Non-proprietary Name	Acoramidis Hydrochloride
Applicant	Alexion Pharma GK
Date of Application	April 17, 2024
Dosage Form/Strength	Each tablet contains 400 mg of acoramidis hydrochloride.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula:	$C_{15}H_{17}FN_2O_3$•HCl
Molecular weight:	328.77
Chemical name:	3-[3-(3,5-Dimethyl-1*H*-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid monohydrochloride

Reviewing Office	Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of transthyretin amyloid cardiomyopathy (wild-type and variant), 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 condition. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Indication

Transthyretin amyloid cardiomyopathy (wild-type and variant)

Dosage and Administration

The usual adult dosage is 800 mg of acoramidis hydrochloride administered orally twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 6, 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	Beyonttra Tablets 400 mg
Non-proprietary Name	Acoramidis Hydrochloride
Applicant	Alexion Pharma GK
Date of Application	April 17, 2024
Dosage Form/Strength	Each tablet contains 400 mg of acoramidis hydrochloride.

Proposed Indication

Transthyretin amyloid cardiomyopathy (wild-type and hereditary)

Proposed Dosage and Administration

The usual adult dosage is 800 mg of acoramidis hydrochloride administered orally twice daily.

Table of Contents

List of Abbreviations

See Appendix.

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

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of amyloidosis caused by deposition of transthyretin (TTR)-derived amyloids in tissues, which mainly occurs in cardiac muscles and leads to functional disorders. TTR is known to be present not only as a wild-type protein with the normal amino acid sequence but also as a variant protein that enhances fibril formation. Irrespective of TTR gene mutation, ATTR-CM can lead to symptoms typical of restrictive cardiomyopathy as well as conduction disorders including bundle branch block, atrioventricular block, and atrial fibrillation, with a poor prognosis in general. Most of the patients experience sudden cardiac death or fatal events such as congestive heart failure and myocardial infarction (*Am J Med.* 1996;101:395-400, *Mayo Clin Proc.* 1984;59:547-55).

Beyonttra Tablets 400 mg is presented as an oral formulation with the active ingredient of acoramidis hydrochloride discovered by Eidos Therapeutics, Inc. Acoramidis binds to TTR tetramer engaged in transport of thyroxine (T_4) and the retinol-retinol-binding protein complex and thereby inhibits its dissociation into monomers, consequently preventing TTR from undergoing degeneration and forming insoluble fibrillar proteins (amyloid fibril).

Clinical development of acoramidis hydrochloride (hereinafter referred to as “acoramidis”) began in 2017 at Eidos Therapeutics, Inc. The US approved acoramidis in November 2024 for the indication of ATTR-CM. As of November 2024, approval reviews are underway in Europe and Brazil.

In Japan, the applicant started clinical development of acoramidis in 2020 and has submitted the application for marketing approval for the proposed indication of “transthyretin amyloid cardiomyopathy (wild-type and hereditary)” based on the results from Japanese and foreign phase III studies.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to brown solid. The general properties of the drug substance, including description, crystalline polymorphism, distribution coefficient, melting point, hygroscopicity, acid dissociation constant, and solubility, have been determined. The commercial manufacturing process produces only crystalline form [redacted], which stability has been demonstrated at room temperature.

Its chemical structure has been elucidated by elemental analysis, nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), infrared absorption spectroscopy (IR), ultraviolet-visible spectrophotometry (UV/VIS), mass spectrometry (MS), and [redacted].

2.1.2 Manufacturing process

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

Based on the following investigations, the quality control strategy has been established (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and design of experiments method

Table 1. Summary of control strategy of drug substance

CQA	Control method
Appearance	Manufacturing process, specifications
Identification	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Content ([redacted])	Manufacturing process, specifications
Purity/organic impurities	Manufacturing process, specifications
Water content	Manufacturing process, specifications
Residual solvents	Manufacturing process, specifications
Residue on ignition	Manufacturing process, specifications

Synthesization processes of [redacted] and [redacted] have been respectively defined as critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include the content, description (appearance), identification (IR, high performance liquid chromatography [HPLC]), [redacted] ([redacted]), purity (organic impurities [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows the main stability studies conducted with the drug substance. The results have shown that the drug substance is stable. In addition, photostability testing has shown that the drug substance is stable to light.

Table 2. Main stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	Double-layered [redacted] PE bag + [redacted] PE container	36 months
Accelerated		40°C	75% RH		6 months

Based on the above, in accordance with Guideline on Evaluation of Stability Data (ICH Q1E guideline), a retest period of [redacted] months has been proposed for the drug substance when stored in the double-layered [redacted] polyethylene (PE) bags, which are then placed in [redacted] PE containers, at room temperature. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet, each containing 400 mg of the drug substance. The drug product also contains microcrystalline cellulose, croscarmellose sodium, hydrated silicon dioxide, magnesium stearate, and Opadry [redacted] White as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through the process consisting of dry granulation, final blending, tableting, film-coating, and packaging/labeling/storage/testing. The tableting process has been defined as a critical step. Process control items and process control values are specified for tableting, film-coating, and packaging/labeling/storage/testing.

Based on the following investigations, the quality control strategy has been established (Table 3):

- Identification of CQAs
- Identification of CPPs based on quality risk assessment and design of experiments method

Table 3. Summary of control strategy of drug product

CQA	Control method
Appearance	Manufacturing process, specifications
Identification	Specifications
Strength	Manufacturing process, specifications
Uniformity of dosage units	Manufacturing process, specifications
Dissolution	Manufacturing process, specifications
Impurities	Manufacturing process, specifications
Microbial limit	Manufacturing process

2.2.3 Control of drug product

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

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted with the drug product. The results have shown that the drug product is stable. In addition, photostability testing has shown that the drug product is stable to light.

Table 4. Main stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial production scale batches	25°C	60% RH	blister pack[a] products	24 months
Accelerated		40°C	75% RH		6 months

a Consisting of a 3-layer film made of polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE)/PVC and aluminum foil

Based on the above, in accordance with the ICH Q1E guideline, a shelf life of 36 months has been proposed for the drug product when packaged in a blister pack consisting of a 3-layer film made of polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE)/PVC and aluminum foil and stored at room temperature. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

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

In this section, doses of acoramidis are expressed as the free base.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Crystal structure of complex of TTR tetramer and acoramidis (CTD 4.2.1.1-9)

X-ray crystallography of co-crystal of TTR variant (TTRv) with amino acid substitution of V122I and acoramidis and modeling of the complex of wild-type TTR (TTRwt) and acoramidis were performed. Acoramidis was shown to form salts by binding to 2 T_4 binding sites of the TTR tetramer, lysine (Lys)15 and Lys15', and also form hydrogen bonds with 2 serine (Ser) residues of the adjacent TTR monomer subunits, adjacent to the opposite side of the binding cavity, Ser117 and Ser117'.

3.1.1.2 Binding affinity of acoramidis to TTR (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3, 4.2.1.1-4)

Binding affinity of acoramidis (0.006-12.5 μmol/L) to human plasma TTRwt was investigated by fluorescence anisotropy,[1)] and the apparent dissociation constant (K_{app}) was determined to be 193 nmol/L.[2)]

The binding affinity of acoramidis (25 μmol/L) to human plasma TTRwt was investigated by isothermal titration calorimetry,[3)] and the dissociation constants to 2 T_4 binding sites (K_{d1} and K_{d2}) were determined to be 4.8 and 314 nmol/L, respectively.

The binding affinity of acoramidis (3.91-1000 nmol/L) to recombinant human TTRwt and human plasma TTRwt was investigated by a surface plasmon resonance method, and the dissociation rate constant (k_{off}) and association rate constant (k_{on}) were determined to be 0.02 ± 0.002 s^{-1} and $1.3 \pm 0.3 \times 10^6$ $(mol/L)^{-1}s^{-1}$, respectively, with the residence time (τ) of 51 ± 5 s and dissociation constant (K_d) of 16 ± 2 nmol/L.[4)]

The binding affinity of acoramidis (0.3-10000 nmol/L) to recombinant human TTRwt was investigated by microscale thermophoresis, and the K_d (mean ± standard deviation [SD]) was determined to be 26 ± 7 nmol/L.

3.1.1.3 Binding of acoramidis to and stabilizing of human serum or plasma TTR (CTD 4.2.1.1-5, 4.2.1.1-6, 4.2.1.1-7)

The binding of acoramidis (1.25-80 μmol/L) to human serum TTR was investigated by a fluorescent probe exclusion (FPE) method,[5)] and the occupancy of acoramidis to TTRwt increased in a concentration-dependent manner. The binding of acoramidis (10 μmol/L) to TTRwt (5 μmol/L) was not inhibited by addition of albumin (600 μmol/L), transferrin (25 μmol/L), fibrinogen (5 μmol/L), or immunoglobulin G (IgG) (70 μmol/L).

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1) Acoramidis was added to a buffer solution containing TTR and TTR ligand labeled with fluoresceinisothiocyanate (FITC) (fluorescence polarization probe) to measure changes in fluorescence polarization associated with dissociation of the concerned TTR ligand from the TTR. From the measured changes, the binding affinity of acoramidis to TTR was determined.

2) Mean of results from 3 replicates of measurement

3) A solution of acoramidis (25 μmol/L) in phosphate buffer was added dropwise to a phosphate buffer solution containing purified TTR, and calorie released during interaction between acoramidis and TTR tetramer was measured.

4) Mean ± SD of results from 4 assays (consisting of 3 assays with recombinant human TTRwt and 1 with human plasma TTRwt)

5) In this assay, a chemical compound that emits fluorescence when selectively binding to the Lys residue at the T_4 binding site of TTR was used as a probe, and to a buffer solution containing TTR and the concerned probe, acoramidis was added to measure a subsequent reduction in fluorescence intensity. Using the resultant reduction rate as an indicator, the binding rate of acoramidis to TTR was determined.

Serum samples collected from patients with variant ATTR-CM (ATTRv-CM) (n = 54)[6] and human serum pool from donors with TTRwt were subjected to the FPE assay, and TTR occupancy[7] of acoramidis (10 μmol/L) to 12 TTRv proteins was determined. TTR occupancy of acoramidis to all TTRv proteins investigated exceeded 90% (Table 5).

Table 5. TTR occupancy (%) of acoramidis by TTR genotype

Disease type	Genotype	Number of samples	TTR occupancy (%)
Variant type	G6S	2	98.71, 100.91[a]
	A25S	1	109.51[a]
	V30M	1	100.34[a]
	A36D	1	110.27[a]
	E42D	1	100.05[a]
	S50R	1	99.11[a]
	T60A	4	100.12 ± 1.77
	I68L	7	99.18 ± 3.16
	E89Q	1	96.44[a]
	E92Q	1	98.46[a]
	V94L	1	90.13[a]
	V122I	33	105.63 ± 15.31
Wild type		Human serum pool[b]	99.37 ± 1.77

Mean ± SD

a Individual value; b, From healthy adults, unknown sample size

Plasma samples collected from patients with ATTRv-CM (n = 64)[6] and human plasma pool from donors with TTRwt were subjected to a western blot (WB) method, and TTR stabilization rates[8] of acoramidis (10 μmol/L) to 18 TTRv proteins were determined. TTR stabilization rates of acoramidis to all TTRv proteins investigated exceeded 90% (Table 6).

6) Collected from patients with ATTR-CM in Study AG10-301

7) TTR occupancy of acoramidis was determined based on a reduction rate in fluorescence intensity associated with addition of acoramidis to a buffer solution containing TTR and a probe in comparison with the negative control.

8) Plasma samples with acoramidis or dimethyl sulfoxide (DMSO) added were treated in an acid buffer solution for 72 hours, and a reduction rate in TTR tetramer from baseline was determined. Based on the reduction rate, the TTR stabilization rate of acoramidis was calculated.

Table 6. TTR stabilization rate (%) of acoramidis by TTR genotype

Disease type	Genotype	Number of samples	TTR stabilization rate (%)	
			DMSO	Acoramidis
Variant type	G6S	2	28.17, 28.36[a]	88.39, 103.48[a]
	A25S	1	20.88[a]	115.43[a]
	V30M	2	31.95, 20.67[a]	81.73, 124.82[a]
	A36D	1	50.54[a]	104.20[a]
	E42D	1	24.14[a]	109.63[a]
	S50R	1	12.37[a]	66.84[a]
	T60A	4	22.93 ± 5.46	106.40 ± 21.25
	I68L	7	21.38 ± 7.61	98.53 ± 9.39
	E89Q	1	26.96[a]	82.23[a]
	E92Q	1	25.89[a]	107.21[a]
	V94L	1	25.96[a]	92.79[a]
	V122I	36	24.86 ± 12.60	89.91 ± 11.93
	A97S	1	19.69[a]	95.87[a]
	D38A	1	11.92[a]	103.03[a]
	F64L	1	6.02[a]	105.76[a]
	L58H	1	10.46[a]	107.54[a]
	P24S	1	11.44[a]	113.17[a]
	Y114C	1	1.95[a]	86.57[a]
Wild type		7 (human plasma pool[b])	21.75 ± 1.93	108.42 ± 13.98

Mean ± SD
a Individual value
b From healthy adults

3.1.2 *In vivo* studies

3.1.2.1 Occupancy of acoramidis to TTR in dog serum (CTD 4.2.2.7-1, 4.2.3.2-5 [reference data])

A single dose of acoramidis (5 or 20 mg/kg) was administered orally to male and female dogs (n = 2/group), and blood samples were collected before administration and at 2, 4, 6, 8, 12, and 24 hours after administration to determine TTR occupancy in serum by the FPE method. The results suggested that TTR occupancy increased in a manner dependent on plasma acoramidis concentrations.

Acoramidis (50, 100, or 200 mg/kg) or vehicle (0.5%w/v methylcellulose solution) was administered orally to male and female dogs (n = 2 or 6/group)[9)] for 7 days, and blood samples were collected before administration on Day 1 as well as before administration and at 1 hour after administration on Day 7 to determine TTR occupancy in serum by the FPE method. The results showed that TTR occupancy exceeded 90% in all groups at 1 hour after administration on Day 7.

3.1.2.2 Occupancy of acoramidis to TTR tetramer in monkey serum (CTD 4.2.2.2-9)

A single dose of acoramidis (5 mg/kg) was administered orally to male cynomolgus monkeys (n = 3/group), and blood samples were collected at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours after administration to determine TTR occupancy in serum by the FPE method. The results showed that TTR occupancy >66% was maintained until 12 hours after administration of acoramidis.

9) n = 2/group for the acoramidis 50 and 100 mg/kg groups and n = 6/group for the acoramidis 200 mg/kg and vehicle groups

3.2 Secondary pharmacodynamics

3.2.1 Effects on cell viability and growth (CTD 4.2.1.2-7)

Human hepatoma Hep3B cells, human acute T-cell leukemia Jurkat cells, human breast cancer MCF7 cells, and human cervical cancer HeLa cells treated with acoramidis (1-100 μmol/L) were assessed for their cell viability and growth in an assay using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) as an indicator (MTT assay). The results showed that acoramidis was not cytotoxic or antiproliferative in any cell line.

3.2.2 Off-target effects on various enzymes, receptors, ion channels, and transporters (CTD 4.2.1.2-1, 4.2.1.2-2 [reference data], 4.2.1.2-3, 4.2.1.2-4, 4.2.1.2-5, 4.2.1.2-6)

The inhibitory activity of acoramidis (10-100 μmol/L) against 84 types of enzymes, receptors, ion channels, and transporters was investigated. The results showed that acoramidis did not inhibit any potential target molecule by >50%.

3.2.3 Pharmacological effects of metabolites (CTD 4.2.1.2-8, 4.2.1.2-9 [reference data])

The major metabolite of acoramidis in humans is acylglucuronate conjugate, and the apparent binding affinity of the acylglucuronate conjugate to TTRwt in human plasma (K_{app} = 1102 nmol/L) was lower than that of acoramidis (K_{app} = 241 nmol/L). The stabilization rate of the acylglucuronate conjugate to TTRwt in human plasma was 24% to 34% of that of acoramidis.

3.3 Safety pharmacology

Table 7 shows results from safety pharmacology studies.

Table 7. Summary of safety pharmacology studies

Item	Test system	Parameters and methods	Dose	Route of administration	Findings	CTD
Central nervous	Rat (SD) (8 males/group)	Modified Irwin method	Acoramidis 0,[a] 100, 300, 1000 mg/kg Single dose	Oral	No effects	4.2.1.3-3
Cardiovascular	HEK293 cells stably expressing hERG channel	hERG current	Acoramidis 0,[b] 10, 50 μmol/L	*In vitro*	hERG current was inhibited by -3.2%, 3.2%, and 2.1% at 0, 10, and 50 μmol/L, respectively	4.2.1.3-2
	Dog (beagle) (4 males)	Blood pressure, heart rate, electrocardiogram (telemetry)	Acoramidis 0,[a] 50, 200, 600 mg/kg Single dose[c]	Oral	600 mg/kg: Blood pressure decreased, heart rate increased, PR interval shortened, QT interval shortened	4.2.1.3-5
Respiratory	Rat (SD) (8 males/group)	Tidal volume, respiratory rate, minute volume	Acoramidis 0,[a] 100, 300, 1000 mg/kg Single dose	Oral	No effects	4.2.1.3-4

a 0.5% (w/v) methylcellulose solution
b 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffered saline containing 0.3% (v/v) dimethyl sulfoxide (DMSO)
c Conducted as a 4-treatment 4-period crossover study with a washout period of 7 days

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of acoramidis

The applicant's explanation about mechanism of action of acoramidis on wild-type or variant ATTR-CM:

ATTR-CM is caused by deposition of TTR-derived amyloid fibrils in the cardiac muscle, and these TTR-derived amyloid fibrils are aggregates of misfolded TTR monomers released by dissociation of TTR tetramers destabilized due to aging or gene mutations. Of ≥150 TTR gene mutations identified in humans up to date, 36 mainly cause cardiomyopathy (*Neurochem Int.* 2022;155:105313). In view of the following points, acoramidis is expected to inhibit amyloid fibril formation in patients with ATTR-CM by stabilizing both TTRwt and TTRv tetramers: (1) TTRwt and major TTRv proteins are considered to cause cardiac amyloidosis via a common mechanism; and (2) *in vitro* studies using human serum showed that the binding and stabilization rates of acoramidis were high for TTRwt and all TTRv proteins investigated [see Section "3.1.1.3 Binding of acoramidis to and stabilizing of human serum or plasma TTR"].

In view of the applicant's explanation, PMDA considers that acoramidis can be expected to stabilize TTR irrespective of TTR gene mutation and type of the gene mutation.

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

Plasma acoramidis concentrations were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 0.240, 0.200, 0.200, 0.018, and 0.240 μg/mL in specimens from mice, rats, dogs, monkeys, and rabbits, respectively. Radioactivity after administration of ^{14}C-acoramidis was determined by quantitative whole-body autoradiography or using a liquid scintillation counter.

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed as mean or mean ± SD. In this section, unless otherwise specified, doses of acoramidis are expressed as the free base.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Mouse (CTD 4.2.2.2-1)

A single dose of acoramidis was administered orally to male mice, and the PK parameters are shown in Table 8.

Table 8. PK parameters in male mice after single oral administration of acoramidis

Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
25	3/timepoint	4.90	0.500	40.2
50	3/timepoint	16.5	0.500	57.7
100	3/timepoint	78.7	0.500	114
200	3/timepoint	254	0.500	311

4.1.1.2 Rat (CTD 4.2.2.2-4)

A single dose of acoramidis was administered orally to male rats, and the PK parameters are shown in Table 9.

Table 9. PK parameters in male rats after single oral administration of acoramidis

Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max}[b] (h)	AUC_{0-24h} (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
5[a]	3	2.083 ± 0.358	1.00	22.506 ± 3.539	29.065 ± 3.381	11.9 ± 2.42

a Amount of acoramidis hydrochloride
b Median

4.1.1.3 Rabbit (CTD 4.2.2.2-5)

A single dose of acoramidis was administered orally to female rabbits, and the PK parameters are shown in Table 10.

Table 10. PK parameters in female rabbits after single oral administration of acoramidis

Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max}[a] (h)	AUC_{0-24h} (μg·h/mL)
25	3	18.5 ± 6.63	0.500	106 ± 19.1
75	3	56.3 ± 2.91	1.00	233 ± 5.79
150	3	94.3 ± 29.6	1.00	367 ± 78.9

a Median

4.1.1.4 Mouse, rat, dog, and monkey (CTD 4.2.2.2-2, 4.2.2.2-3, 4.2.2.2-6, 4.2.2.2-9)

A single dose of acoramidis was administered intravenously or orally to male mice, male rats, male dogs, and male monkeys, and the PK parameters are shown in Table 11.

Table 11. PK parameters in male mice, male rats, male dogs, and male monkeys after single intravenous or oral administration of acoramidis

Animal species	Route of administration	Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	BA (%)	V_{ss} (L/kg)	CL (L/h/kg)
Mouse	Intravenous	1	3	2.17 ± 0.225	0.500	17.0 ± 4.31	5.32 ± 0.617	-	0.392 ± 0.107	0.0613 ± 0.0148
	Oral	5	3	2.78 ± 0.0954	1.00	25.9 ± 1.30	5.82 ± 1.08	30.5	-	-
Rat	Intravenous	1	3	3.76 ± 0.372	0.083	38.2 ± 8.74	12.9 ± 3.40	-	0.488 ± 0.0614	0.0270 ± 0.00558
	Oral	5	3	4.31 ± 0.312	2.00	114 ± 36.45	12.5 ± 0.538	59.7	-	-
Dog	Intravenous	1	3	4.47 ± 0.405	0.083	46.1 ± 4.70	19.4 ± 7.64	-	0.612 ± 0.141	0.0219 ± 0.00234
	Oral	5	3	4.10 ± 1.59	0.500	91.1 ± 34.6	20.0 ± 8.60	39.5	-	-
Monkey	Intravenous	1	3	6.45 ± 1.95	0.083	25.7 ± 9.72	10.1 ± 2.15	-	0.525 ± 0.0979	0.0423 ± 0.0136
	Oral	5	3	3.60 ± 1.51	1.00	63.5 ± 11.8	13.2 ± 1.19	49.4	-	-

-, Not calculated
a Median

4.1.1.5 Rat and dog (CTD 4.2.2.5-1, 4.2.2.5-2)

A single dose of ^{14}C-acoramidis was administered orally to male and female rats and male and female dogs, and the PK parameters are shown in Table 12.

Table 12. PK parameters in male and female rats and male and female dogs after single oral administration of acoramidis

Animal species	Sex	Dose (mg/kg)	Number of animals	C_{max} (ng eq/g)	t_{max} (h)	$AUC_{0-\infty}$ (ng eq·h/g)	$t_{1/2}$ (h)
Rat	Male	1000	3/timepoint	402000	1.00	4610000	9.53
	Female	1000	3/timepoint	565000	4.00	8790000	26.7
Dog	Male	250	3	237000, 64500[a]	6.00, 8.00[a]	2190000, 1200000[a]	60.1, 62.0[a]
	Female	250	3	282000 ± 50500	6.00[b]	3510000 ± 814000	62.4 ± 22.2

a Individual values (excluding 1 animal which vomited after administration of ^{14}C-acoramidis)
b Median

4.1.2 Repeated-dose studies

4.1.2.1 Mouse (CTD 4.2.3.4.2-1)

Acoramidis was administered orally to male and female mice once daily for 4 weeks, and the PK parameters are shown in Table 13.

Table 13. PK parameters in male and female mice after repeated oral administration of acoramidis

Dose (mg/kg/day)	Measurement timepoint (Day)	C_{max} (µg/mL)		AUC_{0-24h} (µg·h/mL)	
		Male	Female	Male	Female
500	1	510	514	1850	2100
	28	378	271	969	1310
1000	1	437	533	3370	4750
	28	558	403	1730	1970
1500	1	666	793	1090	1200
	28	-	-	-	-

n = 2-3/sex/timepoint; -, Not calculated

4.1.2.2 Rat (CTD 4.2.3.2-2, 4.2.3.2-4)

Acoramidis was administered orally to male and female rats once daily for 4 or 26 weeks, and the PK parameters are shown in Table 14.

Table 14. PK parameters in male and female rats after repeated oral administration of acoramidis

Treatment duration	Dose (mg/kg/day)	Measurement timepoint (Day)	C_{max} (µg/mL)		AUC_{0-24h} (µg·h/mL)	
			Male	Female	Male	Female
4 weeks	50	1	11.3	40.4	110	110
		26	35.7	68.6	145	123
	200	1	69.3	127	334	624
		26	130	294	562	1060
	600	1	145	254	1260	2300
		26	216	378	1810	2810
	1000	1	172	280	2440	3170
		26	356	364	5180	4460
26 weeks	50	1	13.6	20.1	95.6	91.8
		182	56.5	126	141	171
	300	1	123	181	731	849
		182	182	361	1560	1930
	600	1	183	174	1280	1620
		182	267	406	2780	3490

n = 3/sex/timepoint

4.1.2.3 Dog (CTD 4.2.3.2-7, 4.2.3.2-9)

Acoramidis was administered orally to male and female dogs once daily for 4 or 39 weeks, and the PK parameters are shown in Table 15.

Table 15. PK parameters in male and female dogs after repeated oral doses of acoramidis

Treatment duration	Dose (mg/kg/day)	Measurement timepoint (Day)	Number of animals	C_{max} (µg/mL)		AUC_{0-t}[a] (µg·h/mL)	
				Male	Female	Male	Female
4 weeks	50	1	3	33.9 ± 9.65	32.6 ± 9.12	156 ± 58.8	152 ± 16.5
		28	3	42.6 ± 10.0	42.0 ± 3.05	160 ± 26.9	182 ± 14.5
	200	1	3	90.9 ± 14.9	127 ± 36.5	574 ± 49.8	775 ± 216
		28	3	130 ± 100	114 ± 3.00	796 ± 673	607 ± 106
	400	1	3	213 ± 54.9	111 ± 92.0	1700 ± 695	935 ± 828
		28	3	212 ± 149	317 ± 42.9	1140 ± 880	1740 ± 189
	600	1	5	232 ± 129	176 ± 137	1700 ± 1360	1700 ± 1480
		28	5	336 ± 101[b]	411 ± 69.8	1820 ± 571[b]	2810 ± 579
39 weeks	50	1	4	22.8 ± 2.49	26.4 ± 3.24	90.1 ± 16.1	91.3 ± 13.7
		273	4	48.2 ± 9.94	61.0 ± 6.30[c]	150 ± 17.0	159 ± 23.8[c]
	112	1	4	45.8 ± 7.61	60.9 ± 24.5	238 ± 32.8	282 ± 177
		273	4	105 ± 11.7	118 ± 30.1[c]	353 ± 43.2	472 ± 116[c]
	250	1	6	147 ± 43.3	146 ± 45.5	818 ± 181	830 ± 169
		273	5	233 ± 53.1	264 ± 77.2	1040 ± 203	1310 ± 238

a AUC_{0-24h} in the 4-week study and AUC_{0-12h} in the 39-week study
b n = 4
c n = 3

4.1.2.4 Rabbit (CTD 4.2.3.5.2-4)

Acoramidis was administered orally to pregnant rabbits once daily on Gestation Days 6 to 13, and the PK parameters are shown in Table 16.

Table 16. PK parameters in pregnant rabbits after repeated oral administration of acoramidis

Dose (mg/kg/day)	Measurement timepoint	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)
25	Gestation Day 13	19.7	147
75	Gestation Day 13	117	410
200	Gestation Day 13	319	1400

n = 3/timepoint

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.5-1)

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to male pigmented rats, and radioactivity concentrations in each tissue were determined at 0.5, 4, 8, 24, 48, 72, and 168 hours post-dose by whole-body autoradiography (n = 1/timepoint). The radioactivity concentration peaked at 0.5 hours post-dose in all tissues evaluated, except for the epididymis, eye lens, turbinate, and testis in which it peaked at 8 hours post-dose. The tissues with the maximum radioactivity concentration higher than that in blood (247000 ng eq/g) were liver (554000 ng eq/g), artery wall (277000 ng eq/g), and adrenal gland (260000 ng eq/g). Concentrations of radioactivity distributed in the melanin-containing tissues (eye and skin) were lower than that in blood, and the radioactivity concentrations at 24 hours post-dose were below the lower limit of quantification. The radioactivity concentrations in all tissues evaluated decreased below the lower limit of quantification by 168 hours post-dose.

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to male albino rats, and radioactivity concentrations in each tissue were determined at 0.5, 4, 8, 24, and 72 hours post-dose by whole-body autoradiography (n = 1/timepoint). The radioactivity concentration peaked at 4 hours post-dose in all tissues evaluated, except for the adrenal gland and brain choroid plexus in which it peaked at 0.5 hours post-dose. The tissues with the maximum radioactivity concentration higher than that in blood (128000 ng eq/g) were liver (419000 ng eq/g), artery wall (143000 ng eq/g), and renal cortex

(140000 ng eq/g). The radioactivity concentrations in all the tissues evaluated, except for the cecum and liver, decreased below the lower limit of quantification by 72 hours post-dose.

4.2.2 Plasma protein binding (CTD 4.2.2.3-1)

Acoramidis 10 or 50 μmol/L was added with plasma specimens from rats, dogs, and monkeys, and the plasma protein binding rates were 92.3% to 97.8%, 86.8% to 94.8%, and 97.0% to 98.8%, respectively.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-2)

Acoramidis 0.1, 1, or 10 μmol/L was added with blood specimens from rats, dogs, and monkeys, and the blood/plasma concentration ratios were 0.64 to 0.70, 0.48 to 0.56, and 0.56 to 0.71, respectively.

4.2.4 Placental transfer

Placental transfer of acoramidis has not been investigated. The applicant explained that in a study for prenatal and postnatal development including maternal function in rats, embryo resorption and abnormal labor were observed, suggesting that acoramidis may cross the placenta and be distributed to the fetuses.

4.2.5 Distribution in central nervous system (CTD 4.2.2.3-3)

A single dose of acoramidis 200 mg/kg was administered orally to male rats (n = 3/timepoint), and acoramidis concentrations in the brain and cerebrospinal fluid at 1, 4, 12, and 24 hours were determined to be <1.1% of the plasma concentration.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-2, 4.2.2.4-3)

Acoramidis 10 μmol/L was added with mouse, rat, dog, and monkey hepatocytes, and acylglucuronate conjugate of acoramidis was identified as the main metabolite for any animal species.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma (CTD 4.2.2.5-1, 4.2.2.5-2)

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to male and female rats (n = 3/sex), and the most abundant radioactive compound in plasma was unchanged acoramidis[10)] (accounting for 60.7% and 70.9% of $AUC_{0\text{-}48h}$ of radioactivity in plasma in males and females, respectively). Metabolites identified are acylglucuronate conjugates of acoramidis (M4,[11)] 24.6% and 16.1%; M3, 2.04% and 1.76%; M2, 1.14% and 0.906%; and M1, 0.701% and 0.438%), M8 (oxidized form of acoramidis)/M9 (glucuronate conjugate of the oxidized form of acoramidis)[12)] (0.884% and 0.542%), and M13 (oxidized form of acoramidis) (0.766% and 1.12%).

A single dose of ^{14}C-acoramidis 250 mg/kg was administered orally to male and female dogs (n = 3/sex), and the most abundant radioactive compound in plasma was unchanged acoramidis[10)] (accounting for 56.3% and 47.2% of $AUC_{0\text{-}24h}$ of radioactivity in plasma in males and females, respectively). Metabolites

[10)] Unchanged acoramidis was eluted together with M10 (glucuronate conjugate of acoramidis) and M11 (oxidized form of acoramidis), but the co-elution peak was mainly consisting of unchanged acoramidis.
[11)] M4 was eluted together with M5 (glycine conjugate of acoramidis) and M6 (oxidized form of acoramidis), but the co-elution peak was mainly consisting of M4.
[12)] M8 and M9 were co-eluted.

identified are acylglucuronate conjugates of acoramidis (M4,[13] 14.0% and 44.6%; M3, 1.76% and 3.02%; M2, 0.622% and 0.661%; and M1, 0.337% and 0.633%), M8/M9[12] (0.667% and 0.253%), and M13 (0.667% and 0%).

4.3.2.2 Metabolites in urine, feces, and bile (CTD 4.2.2.5-1, 4.2.2.5-2)

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to male and female rats (n = 3/sex). Unchanged acoramidis[14] excreted into urine until 72 hours post-dose accounted for 6.59% and 15.7% of the radioactivity administered in males and females, respectively. The metabolites identified are M13 (4.69% and 5.07%), M8 (2.06% and 1.34%), acylglucuronate conjugates of acoramidis (M4,[11] 0.988% and 0.302%; M3, 0.546% and 0.570%; and M2, 0.0477% and 0.259%), and M12 (unknown chemical structure) (0.207% and 0%). Unchanged acoramidis[14] excreted into feces accounted for 61.5% in males and 54.9% in females. The metabolites identified are acylglucuronate conjugates of acoramidis (M1, 2.16% and 1.69%; M3/M5/M6,[15] 1.96% and 1.25%; and M2, 0.357% and 0.566%), M16 (unknown chemical structure) (2.39% and 0.976%), M13 (1.91% and 1.22%), M15 (unknown chemical structure) (0.647% and 0.683%), and M14 (unknown chemical structure) (0.513% and 0.735%).

A single dose of ^{14}C-acoramidis f1000 mg/kg was administered orally to bile duct-cannulated male rats (n = 3), and unchanged acoramidis[14] excreted into bile until 48 hours post-dose accounted for 8.84%. The metabolites identified are acylglucuronate conjugates of acoramidis (M4,[11] 30.4%; M2, 18.6%; M3, 9.02%; M1, 7.27%; and M7, 1.95%) and M16 (2.01%). Unchanged acoramidis[14] excreted into feces accounted for 4.93%, and the metabolites identified are M3/M5/M6[15] (1.08%) and M14 (0.141%).

A single dose of ^{14}C-acoramidis 250 mg/kg was administered orally to male and female dogs (n = 3/sex), and unchanged acoramidis[10] excreted into urine until 168 hours post-dose accounted for 19.8% in males and 14.0% in females. The metabolites identified are M13 (1.73% and 0.921%), acylglucuronate conjugates of acoramidis (M3, 0.543% and 1.18%; M4,[13] 0.389% and 7.86%; M1, 0.135% and 0.507%; M2, 0.113% and 0.361%), and M8/M9[12] (0.182% and 0.327%). Unchanged acoramidis[14] excreted into feces accounted for 43.9% in males and 71.2% in females, and the metabolite identified is M13 (0.522% and 0.421%).

4.4 Excretion

4.4.1 Excretion into urine, feces, and bile (CTD 4.2.2.5-1, 4.2.2.5-2)

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to male and female rats (n = 3/sex), and the radioactivity excreted into urine until 168 hours post-dose accounted for 16.3% and 24.8% of the radioactivity administered in males and females, respectively, and the radioactivity excreted into feces accounted for 79.0% and 71.7%, respectively.

A single dose of ^{14}C-acoramidis 1000 mg/kg was administered orally to bile duct-cannulated male rats (n = 3), and the radioactivity excreted into urine, feces, and bile until 120 hours post-dose accounted for 9.79%, 5.98%, and 80.5%, respectively.

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[13] M4 was eluted together with M6, but the co-elution peak mainly consisted of M4.
[14] Unchanged acoramidis was eluted together with M11, but the co-elution peak mainly consisted of unchanged acoramidis.
[15] M3, M5, and M6 were co-eluted.

A single dose of ^{14}C-acoramidis 250 mg/kg was administered orally to male and female dogs (n = 3/sex), and the radioactivity excreted into urine until 168 hours post-dose accounted for 34.4% in males and 27.8% in females, and the radioactivity excreted into feces accounted for 51.0% in males and 66.0% in females.

4.4.2 Transfer into milk

Transfer of acoramidis into milk has not been investigated. The applicant explained that in the study for prenatal and postnatal development including maternal function in rats, decreased body weight of neonates at weaning was observed, suggesting that acoramidis might be transferred into milk.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the review below, PMDA concluded that non-clinical pharmacokinetics of acoramidis were appropriately evaluated.

4.R.1 Tissue distribution

In the tissue distribution study in rats [see Section "4.2.1 Tissue distribution"], high radioactivity concentrations were observed in the liver, adrenal gland, and kidney. Concerning the finding, PMDA asked the applicant to explain whether distribution of acoramidis or its metabolites in these tissues had a potential to cause safety problems in humans.

The applicant's explanation:
Repeated-dose toxicity studies [see Section "5.2 Repeated-dose toxicity"] did not present changes suggestive of toxicity in the liver or adrenal gland, and thus distribution of acoramidis or its metabolites in the liver or adrenal gland was considered unlikely to cause safety problems. In a 4-week repeated-dose study in mice (non-Good Laboratory Practice [GLP]),[16)] on the other hand, multifocal tubular degeneration/regeneration was observed in males at 1000 mg/kg/day. This finding was severe and accompanied by degenerative or inflammatory changes, and acoramidis was thus considered to have caused the adverse changes in the kidney. However, the $AUC_{0\text{-}24h}$ of acoramidis at the dose relevant to this finding was 1730 μg·h/mL, which was 37 times the AUC_{tau} (47.2 μg·h/mL) in humans receiving acoramidis according to the recommended clinical dosage regimen. In view of this, the above finding is not considered to suggest safety concerns in humans.

Taking account of the submitted non-clinical toxicity study results and applicant's explanation, PMDA considers that distribution of acoramidis or its metabolites in the liver, adrenal gland, and kidney is unlikely to cause safety problems in humans.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data of acoramidis in the form of results from the repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity (phototoxicity) studies.

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16) Acoramidis 0 (0.5% (w/v) methylcellulose solution), 500, 1000, or 1500 mg/kg/day was administered orally to male and female rasH2 mice for 28 days (n = 10/sex/group).

In this section, doses of acoramidis are expressed as the free base.

5.1 Single-dose toxicity

Although no independent single-dose toxicity studies have been conducted, the acute toxicity of acoramidis was evaluated based on the results obtained after the first dose in a 4-week repeated-dose toxicity and *in vivo* genotoxicity studies in rats as well as a 4-week repeated-dose toxicity study in dogs (Table 17). Transient vomiting was observed in dogs, but acoramidis was well tolerated. The approximate lethal doses were >2000 mg/kg in rats and >600 mg/kg in dogs.

Table 17. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	Acoramidis 0,[a] 50, 200, 600, 1000	No remarkable findings	>1000	4.2.3.2-2
Male rats (SD)	Oral	Acoramidis 0,[a] 600, 1000, 2000	No remarkable findings	>2000	4.2.3.3.2-1
Male and female dogs (beagle)	Oral	Acoramidis 0,[a] 50, 200, 400, 600	600: Transient vomiting	>600	4.2.3.2-7

a 0.5% (w/v) methylcellulose solution

5.2 Repeated-dose toxicity

The following studies were conducted: 4-, 13-, and 26-week repeated-dose toxicity studies in rats and 4-, 13-, and 39-week repeated-dose toxicity studies in dogs (Table 18). Decreased body weight was observed as a change attributable to acoramidis and also accompanied by its secondary changes. In the 4- and 13-week repeated-dose toxicity studies in rats, the effect on the kidney was suggested, and in the 4-week repeated-dose toxicity study in dogs, degeneration and necrosis of cardiac muscles were observed in the heart. In the repeated-dose toxicity studies in rats (26 weeks) and dogs (39 weeks), the exposure to acoramidis at the no-observed-adverse-effect level (NOAEL) (600 mg/kg/day in rats, 250 mg/kg/day in dogs) was 2780 μg·h/mL (males) and 3490 μg·h/mL (females) in rats on the basis of $AUC_{0\text{-}24h}$, and 1040 μg·h/mL (males) and 1310 μg·h/mL (females) in dogs on the basis of $AUC_{0\text{-}12h}$, which were 29 (males) and 37 (females) times in rats as well as 22 (males) and 28 (females) times in dogs the AUC_{tau} (47.2 μg·h/mL) in humans receiving acoramidis according to the recommended clinical dose.

Table 18. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	Oral	4 weeks + 2 weeks for recovery	Acoramidis 0,[a] 50, 200, 600, 1000	≥50: Vacuolation in tubular epithelial cells (female) ≥200: Decreased BUN, decreased glucose value (male), increased urine volume ≥600: Increased albumin value (male), decreased globulin value (male), increased A/G ratio (male), decreased Cl value, decreased urinary pH (male), increased liver weight, hepatocyte hypertrophy (male), vacuolation in tubular epithelial cells 1000: Decreased body weight and reduced body weight gain, decreased glucose value, decreased total protein value (female), decreased globulin value, increased A/G ratio, increased ALP value (male), increased frequency of leukocytes present in urine, increased ketone value in urine (male), hepatocyte hypertrophy Reversible	1000	4.2.3.2-2
Male and female rats (SD)	Oral	13 weeks + 2 weeks for recovery	Acoramidis 0,[a] 50, 350, 1000	Death or euthanization in moribund condition: 1000 (1 of 15 males, 2 of 15 females) ≥350: Transparent discharge in oral cavity, decreased monocyte, eosinophil, and neutrophil counts (male), decreased glucose value, decreased BUN value (female), decreased globulin value (male), increased A/G ratio (male), decreased inorganic phosphorus value (male), decreased urinary pH value (female), increased urine volume (male), increased adrenal gland weight (female), increased kidney weight (female), increased liver weight, centrilobular hypertrophy of hepatocytes 1000: Respiratory sound (female), decreased body weight, decreased food consumption, increased white blood cell, lymphocyte, monocyte, eosinophil, basophil, and peroxidase-negative large cell counts (female), decreased fibrinogen value (male), decreased total protein value, increased albumin value (male), decreased albumin value (female), decreased globulin value, increased A/G ratio, increased ALP value, decreased calcium value, increased inorganic phosphorus value, decreased Cl value, decreased urine specific gravity (female), increased urine volume, increased adrenal gland weight, adrenocortical hypertrophy, vacuolation in tubular epithelial cells Reversible	350	4.2.3.2-3
Male and female rats (SD)	Oral	26 weeks + 4 weeks for recovery	Acoramidis 0,[b] 50, 300, 600	≥50: Decreased food consumption (male) ≥300: Salivation; 600: Decreased body weight (male), increased ALP value (male), increased liver weight (female) Reversible (decreased body weight in males continued)	600	4.2.3.2-4
Male and female dogs (beagle)	Oral	4 weeks + 2 weeks for recovery	Acoramidis 0,[a] 50, 200, 400, 600	Death or euthanization in moribund condition: 600 (1 of 5 males) ≥50: Twisting and abnormal vocalization during administration ≥400: Increased heart rate, shortened QT interval, APTT prolongation (female), degeneration of, necrosis of, and inflammatory cell infiltration in cardiac muscles 600: Vomiting, unformed and watery feces, APTT prolongation, increased urine volume, decreased urine specific gravity (female), bleeding and fibril formation in the heart (female), decreased thymic lymphocytes Reversible (the changes in the heart at 600 mg/kg continued)	200	4.2.3.2-7
Male and female dogs (beagle)	Oral	13 weeks + 2 weeks for recovery	Acoramidis 0,[a] 50, 125, 300	≥50: Decreased body weight and reduced body weight gain (male) ≥125: Twisting and hypersalivation during administration, decreased body weight and body weight gain (female), PR interval shortening (female) 300: Vomiting, unformed and watery feces, increased heart rate (male), QT interval shortening (male) Reversible	300	4.2.3.2-8

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female dogs (beagle)	Oral	39 weeks + 4 weeks for recovery	Acoramidis 0,[b] 50, 112, 250	≥112: Decreased red blood cell count (male) 250: Decreased body weight (male), salivation, vomiting, abnormal substance, abnormal feces, increased heart rate, PR interval shortening, decreased hemoglobin and hematocrit values (male), decreased total bilirubin value (male) Reversible (decreased erythroid parameters and decreased total bilirubin value continued)	250	4.2.3.2-9

a 0.5% (w/v) methylcellulose solution
b 0.5% (w/v) carboxymethylcellulose solution

5.3 Genotoxicity

An *in vitro* study of a bacterial reverse mutation assay and an *in vivo* study of a combination micronucleus/alkaline comet assay in rats were conducted (Table 19). Both studies showed acoramidis to be negative, and the applicant explained that acoramidis is unlikely to pose genotoxicity.

Table 19. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate) or dose (mg/kg/day)	Study result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames assay)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537, TA102	S9-	Acoramidis 0,[a] 5, 16, 50, 160, 500, 1600, 5000	Negative	4.2.3.3.1-1
			S9+	Acoramidis 0,[a] 5, 16, 50, 160, 500, 1600, 5000		
In vivo	Combination micronucleus/alkaline comet assay in rats	Male rat (SD) Bone marrow (micronucleus), stomach, liver (comet) Oral administration once daily for 3 days		Acoramidis 0,[b] 600, 1000, 2000	Negative	4.2.3.3.2-1

a DMSO
b 0.5% (w/v) methylcellulose solution

5.4 Carcinogenicity

A 26-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats were conducted (Table 20). No neoplastic lesions attributable to acoramidis occurred in either mice or rats, and the applicant explained that acoramidis is not carcinogenic.

Table 20. Carcinogenicity studies

Test system	Route of administration	Treatment duration	Main lesions	Dose	Acoramidis (mg/kg/day)				Nononcogenic dose (mg/kg/day)	Attached document CTD
					0[a]	30	100	300		
				n Male/female	25/25	25/25	25/25	25/25		
Male and female mice (rasH2)	Oral	26 weeks	Neoplastic lesions		No remarkable findings				300	4.2.3.4.2-2
			Non-neoplastic lesions		No remarkable findings					
Male and female rats (SD)	Oral	104 weeks	Main lesions	Dose Male/female	0[a]/0[a]	5/40	15/120	50/350	Male: 50 Female: 350	4.2.3.4.1-1
				n Male/female	60/60	60/60	60/60	60/60		
			Neoplastic lesions		No remarkable findings					
			Non-neoplastic lesions		Adrenal gland zona fasciculata hyperplasia, islet cell hyperplasia					

a 0.5% (w/v) methylcellulose solution

5.5 Reproductive and developmental toxicity

The following studies were conducted: Studies for fertility and early embryonic development to implantation in rats, for embryo-fetal development in rats and rabbits, and for prenatal and postnatal development including maternal function in rats (Table 21). In the study for prenatal and postnatal development including maternal function in rats, changes attributable to acoramidis observed were embryonic death, decreased body weight in offspring, and learning deficit. The $AUC_{0\text{-}24h}$ (1630 μg·h/mL) of acoramidis at the NOAEL (350 mg/kg/day) in the study for prenatal and postnatal development including maternal function in rats was 17 times the AUC_{tau} (47.2 μg·h/mL) in humans receiving acoramidis according to the recommended clinical dose.

Table 21. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male rats (SD)	Oral	28 days before mating to the day before necropsy	Acoramidis 0,[a] 50, 350, 1000	Death or euthanization in moribund condition: 1000 (3 of 22 animals) ≥350: Rale, reduced body weight gain and body weight 1000: Dehydration, hypersalivation, coarse fur, brown discoloration of face, decreased food consumption, decreased vesicular gland and prostate gland weights, increased epididymis and testis weights	General toxicity: 50 Reproductive potential: 1000	4.2.3.5.1-1
	Female rat (SD)		15 days before mating to Gestation Day 7		Maternal animal: ≥350: Rale 1000: Hypersalivation, reduced body weight gain and body weight, increased food consumption after end of treatment, decreased estrous cycle, prolongation of estrous period Embryo and fetuses: No remarkable findings	General toxicity: 350 Reproductive potential: 1000 Embryo and fetuses: 1000	
Embryo-fetal development	Female rat (SD)	Oral	Gestation Days 6 to 17	Acoramidis 0,[b] 50, 350, 1000	Maternal animal: 1000: Decreased food consumption, reduced body weight gain and body weight, increased food consumption after end of treatment Embryo and fetuses: 1000: Decreased fetal body weight	Maternal animal General toxicity: 1000 Reproductive potential: 1000 Embryo and fetuses: 1000	4.2.3.5.2-2
	Female rabbit (NZW)	Oral	Gestation days 7 to 19	Acoramidis 0,[b] 25, 70, 200	Maternal animal: ≥25: Reduced body weight gain Embryo and fetuses: No remarkable findings	Maternal animal General toxicity: 200 Reproductive potential: 200 Embryo and fetuses: 200	4.2.3.5.2-4
Prenatal and postnatal development including maternal function	Female rat (SD)	Oral	Gestation Day 6 to Lactation Day 20	Acoramidis 0,[b] 50, 350, 1000	Maternal animal: 1000: Death or euthanization in moribund condition (2 of 21 animals), decreased food consumption and body weight, total embryo resorption (3/21 animals) F1 offspring: 1000: Decreased body weight (from birth to post-weaning period), proximal and spatial learning deficits	Maternal animal General toxicity: 350 Reproductive potential: 350 Embryo and fetuses: 350	4.2.3.5.3-1

a 0.5% (w/v) carboxymethylcellulose solution
b 0.5% (w/v) methylcellulose solution

5.6 Other toxicity studies

5.6.1 Phototoxicity study

An *in vitro* phototoxicity study was conducted (Table 22). In view of the results, the applicant explained that acoramidis does not pose phototoxicity.

Table 22. Phototoxicity study

Type of study	Test system	Study method	Result	Attached document CTD
Phototoxicity study	Mouse fibroblast Balb/c 3T3	Cells were exposed to acoramidis at 1.78 to 100 μg/mL for approximately 90 minutes with and without irradiation of UV-A (5 J/cm^2) and UV-B (15 or 21 J/cm^2), and then cell viability was determined.	Non-phototoxic	4.2.3.7.7.1-1

5.6.2 Safety evaluation of impurities

Impurity A was found in the drug substance batches used in the 26-week repeated-dose toxicity study in rats and 39-week repeated dose toxicity study in dogs [see Section "5.2 Repeated-dose toxicity"], and its amount exceeded the qualification threshold defined in the ICH Q3A guideline (Impurities in New Drug Substances). The applicant considered that the concerned impurity poses no problems in terms of general toxicity in view of its intake amounts at the NOAELs in these studies (600 mg/kg/day and 250 mg/kg/day). For the genotoxicity, the concerned impurity was found to present no structural alert in an *in silico* analysis. In addition, this impurity was contained in the drug substance batches used in the carcinogenicity studies in rats and mice [see Section "5.4 Carcinogenicity"], which showed negative results of the NOAELs in these studies (300 mg/kg/day and 350 mg/kg/day) and the obtained negative results. The applicant explained that the concerned impurity poses no problems in terms of genotoxicity.

5.R Outline of the review conducted by PMDA

Based on the submitted data and results from the following review, PMDA concluded that the non-clinical toxicity evaluation presented no findings potentially leading to problems in clinical use of acoramidis, except for findings judged to require raising caution in the following review.

5.R.1 Findings in the heart

Although the changes in the heart (degeneration and necrosis of cardiac muscles) observed in the 4-week repeated-dose toxicity study in dogs were considered to be accidental by the applicant, the concerned changes occurred only in the high-dose acoramidis groups where increased heart rate was also observed in some animals. PMDA asked the applicant to explain a possibility of the continued exercise load in the heart being responsible for these changes.

The applicant's explanation:
The changes in the heart (degeneration and necrosis of cardiac muscles) were observed irrespective of heart rate. A relationship of acoramidis to the changes in the heart cannot be ruled out, although the mechanism of development of the concerned changes remains unknown.

PMDA's view:
The increased heart rate is related to acoramidis and can be one of the causes for the above changes in the heart, but its clinical use is considered unlikely to raise relevant problems because a certain safety

margin is ensured by the following data: The C_{max} (130 μg/mL in males and 114 μg/mL in females) and $AUC_{0\text{-}24h}$ (796 μg·h/mL in males and 607 μg·h/mL in females) of acoramidis at the dose (200 mg/kg/day) not leading to the concerned changes are 9 and 7 times the C_{max} (13.7 μg/mL) and AUC_{tau} (47.2 μg·h/mL), respectively, in humans receiving acoramidis according to the recommended clinical dosage regimen.

5.R.2 Caution in pregnant and lactating women

The study of rat embryo-fetal development revealed fetal toxicity (decreased fetal body weight). The study of rat prenatal and postnatal development including maternal function revealed learning deficits in the offspring in addition to low body weight after birth through the time of weaning. In view of these findings, PMDA requested the applicant to raise caution appropriately through the package insert about the possibility that acoramidis is transferred into milk and crosses the placenta. The applicant responded appropriately.

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

Unless otherwise specified, PK parameters are expressed as mean or mean ± SD. In this section, doses of acoramidis are expressed as the amounts of acoramidis hydrochloride.

6.1 Summary of biopharmaceutic studies and associated analytical methods

The formulation used in a foreign phase III study (Study AG10-301), a Japanese phase III study (Study ALXN2060-TAC-302), and a study for food effect (Study ALXN2060-HV-101) was identical with the to-be-marketed formulation, except for presence or absence of print on the surface.

Plasma acoramidis concentrations were determined by LC-MS/MS, and the lower limit of quantification was 10.0 ng/mL. Stability of TTR in plasma was measured by the FPE method.[5)]

6.1.1 Study for food effect (Study ALXN2060-HV-101, CTD 5.3.3.4-2, study period, July to August 2021)

A 2-treatment, 2-period, crossover study was conducted to investigate the food effect on PK of acoramidis in 18 healthy non-Japanese adults (a ≥14-day washout period). In this study, a single dose of acoramidis 800 mg was administered orally in the fasted or fed state.

The geometric mean ratios [90% confidence interval (CI)] of C_{max} and $AUC_{0\text{-}\infty}$ of acoramidis after administration in the fed state to those in the fasted state were 0.7759 [0.6220, 0.9678] and 0.9287 [0.8641, 0.9982].

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Plasma protein binding (CTD 4.2.2.3-1)

Acoramidis 10 or 50 μmol/L was added with human plasma, and the plasma protein binding rates were 96.5% and 96.3%, respectively.

6.2.1.2 Distribution in blood cells (CTD 4.2.2.3-2)

Acoramidis 0.1, 1, or 10 μmol/L was added with human blood, and the blood/plasma concentration ratios were 0.53, 0.57, and 0.52, respectively.

6.2.1.3 *In vitro* metabolism

6.2.1.3.1 Metabolism of acoramidis (CTD 4.2.2.4-2, 4.2.2.4-3)

Acoramidis 10 μmol/L was added with human hepatocytes, and the main metabolite was an acylglucuronate conjugate of acoramidis, which accounted for 72.5% to 75.8% of the total drug-related substances.

6.2.1.3.2 Identification of UGT isoforms involved in metabolism of acoramidis (CTD 4.2.2.6-6)

Acoramidis 1 or 10 μmol/L was added with human liver microsomes expressing each of human uridine diphosphate-glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B10, and UGT2B15) to investigate the UGT isoforms involved in acylglucuronidation metabolism of acoramidis. The maximum production of acylglucuronate conjugate of acoramidis was found with UGT1A9 (59.9 pmol from acoramidis 1 μmol/L and 467 pmol from acoramidis 10 μmol/L) followed by UGT2B7 (30.0 pmol and 286 pmol) and UGT1A1 (16.6 pmol and 149 pmol) in this order. In view of abundance of each UGT isoform in the human liver (*Drug Metab Dispos.* 2015;43:1331-5) and the urinary excretion rates of unchanged acoramidis and acylglucuronate conjugate of acoramidis in the mass balance study, the contribution rates of UGT2B7, UGT1A9, and UGT1A1 to total clearance of acoramidis were estimated to be 16.3%, 8.67%, and 4.10%, respectively.

6.2.1.4 Inhibition against enzymes

6.2.1.4.1 Inhibition against CYP isoforms (CTD 4.2.2.6-4)

Using human liver microsomes and substrates[17)] of each of the cytochrome P450 (CYP) isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5), a potential of acoramidis at 0.15 to 150 μmol/L (1.1-1100 μmol/L for CYP3A4/5) to inhibit metabolism of the substrate by each CYP isoform was investigated. Against any CYP isoform, 50% inhibitory concentration (IC_{50}) exceeded the highest concentration investigated; IC_{50} values against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were >150 μmol/L, and that against CYP3A4/5 was >1100 μmol/L.

A mixture of human liver microsomes and acoramidis 150 μmol/L was pre-incubated in the presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH) followed by incubation with a substrate[17)] of each of the CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5), and a potential of acoramidis to inhibit each CYP isoform in a time-dependent manner was investigated. Acoramidis inhibited CYP2C8 and CYP2C9 in a time-dependent manner. Furthermore, to investigate the time-dependent inhibitory activity of acoramidis against CYP2C8 and CYP2C9 in detail, a mixture of human liver microsomes and acoramidis (5-150 μmol/L for CYP2C8 and 30-

[17)] Chemical compounds used as substrates of each of the CYP isoforms are as follows: CYP1A2, phenacetin (90 μmol/L); CYP2B6, efavirenz (5 μmol/L); CYP2C8, amodiaquine (2 μmol/L); CYP2C9, diclofenac (12 μmol/L); CYP2C19, *S*-mephenytoin (60 μmol/L); CYP2D6, dextromethorphan (10 μmol/L); CYP3A4/5, midazolam (3 μmol/L) and testosterone (60 μmol/L)

800 μmol/L for CYP2C9) was pre-incubated in the presence or absence of NADPH, followed by incubation with a substrate[18] of each of the CYP isoforms (CYP2C8 and CYP2C9), and time-dependent inhibition parameters (concentration of the inhibitor that yields 50% of the maximum inactivation rate [K_I] and maximum inactivation rate constant [k_{inact}]) were calculated. The K_I and k_{inact} of acoramidis against CYP2C8 were 39 μmol/L and 0.033 min^{-1}, respectively, and those against CYP2C9 were 210 μmol/L and 0.049 min^{-1}, respectively.

6.2.1.4.2 Inhibition against UGT isoforms (CTD 4.2.2.6-7)

Using human liver microsomes and substrates[19] of each of the UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15), a potential of acoramidis at 0.2 to 200 μmol/L to inhibit metabolism of the substrate by each UGT isoform was investigated. Acoramidis inhibited UGT1A9, UGT1A1, and UGT2B7 with the IC_{50} of 150 μmol/L, >200 μmol/L, and >200 μmol/L, respectively.

6.2.1.5 Enzyme induction (CTD 4.2.2.6-5)

Acoramidis 0.15 to 150 μmol/L was added with human hepatocytes (n = 3), and a potential of acoramidis to induce CYP1A2, CYP2B6, and CYP3A4 was investigated. The messenger ribonucleic acid (mRNA) expression levels of CYP1A2, CYP2B6, and CYP3A4 were 0.450% to 2.13%, 2.69% to 5.90%, and 1.62% to 5.40%, respectively, of that induced by the corresponding positive control (CYP1A2, omeprazole 50 μmol/L; CYP2B6, phenobarbital 750 μmol/L; CYP3A4, rifampicin 20 μmol/L).

6.2.1.6 Studies for transporters

6.2.1.6.1 Transport of acoramidis via transporters (CTD 4.2.2.6-10, 4.2.2.6-11)

Acoramidis 1, 10, or 50 μmol/L was added with Caco-2 cells to investigate the permeability. Apparent permeability coefficients (P_{app}) from apical-to-basolateral (A→B) ($P_{app\ A\to B}$) were 0.04×10^{-6} cm/s, 0.04×10^{-6} cm/s, and 0.07×10^{-6} cm/s, respectively, and P_{app} from basolateral-to-apical (B→A) ($P_{app\ B\to A}$) were 17.0×10^{-6} cm/s, 14.0×10^{-6} cm/s, and 12.0×10^{-6} cm/s, respectively, leading to the efflux ratios ($P_{app\ B\to A}/P_{app\ A\to B}$) being 421, 347, and 181, respectively.

Acoramidis 0.3, 3, or 30 μmol/L was added with Madin-Darby canine kidney (MDCK)-II cells expressing P-glycoprotein (P-gp) and those not expressing P-gp, and the efflux ratios ($P_{app\ B\to A}/P_{app\ A\to B}$) of acoramidis were 1.70, 1.53, and 1.38 as well as 1.20, 0.770, and 0.820, respectively. In the presence of a P-gp inhibitor (elacridar 3 μmol/L), the efflux ratio of acoramidis 3 μmol/L was 1.69.

Acoramidis 0.3, 3, or 30 μmol/L was added with MDCK-II cells expressing breast cancer resistance protein (BCRP) and those not expressing BCRP, and the efflux ratios ($P_{app\ B\to A}/P_{app\ A\to B}$) were 22.9, 10.5, and 7.09 as well as 1.43, 0.905, and 0.668, respectively. In the presence of a BCRP inhibitor (Ko143 1 μmol/L), the efflux ratio of acoramidis 3 μmol/L was 1.24.

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[18] Chemical compounds used as substrates of each of the CYP isoforms are as follows: CYP2C8, amodiaquine (20 μmol/L); CYP2C9, diclofenac (120 μmol/L)

[19] Chemical compounds used as substrates of each of the UGT isoforms are as follows: UGT1A1, 17β-estradiol (12 μmol/L); UGT1A3, chenodeoxycholic acid (160 μmol/L); UGT1A4, trifluoperazine (20 μmol/L); UGT1A6, 1-naphthol (2 μmol/L); UGT1A9, propofol (16 μmol/L); UGT2B7, morphine (400 μmol/L); UGT2B15, oxazepam (100 μmol/L)

Acoramidis 0.3, 3, or 30 μmol/L was added with membrane vesicles prepared from Sf9 cells expressing bile salt export pump (BSEP) in the presence or absence of adenosine triphosphate (ATP), and the uptake of acoramidis into vesicles in the presence of ATP was similar to that in the absence of ATP.

Acoramidis 0.3, 3, or 30 μmol/L was added with MDCK-II cells expressing organic anion transporter (OAT)1 and those not expressing OAT1, and the uptake of acoramidis into cells expressing OAT1 was 1.86, 14.2, and 6.15 times, respectively, that into cells not expressing OAT1. In the presence of an OAT1 inhibitor (probenecid 100 μmol/L), the intracellular uptake of acoramidis 3 μmol/L decreased by 87.5%.

Acoramidis 0.3, 3, or 30 μmol/L was added with MDCK-II cells expressing OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug and toxin extrusion (MATE)1, or MATE2-K and those not expressing any of these transporters. The uptake of acoramidis into cells expressing each transporter was similar to that into cells not expressing the transporter, and addition of an inhibitor[20)] against each transporter did not change the intracellular uptake of acoramidis 3 μmol/L.

6.2.1.6.2 Inhibitory activity against transporters (CTD 4.2.2.6-9, 4.2.2.6-14, 4.2.2.6-15)

A potential of acoramidis at 0.05 to 100 μmol/L to inhibit transport of a substrate (digoxin) of P-gp was investigated using Caco-2 cells. Acoramidis did not inhibit transport of digoxin.

Using membrane vesicles prepared from Sf9 cells expressing P-gp, BCRP, or BSEP or MDCK-II cells expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K, and substrates of each of these transporters,[21)] a potential of acoramidis (30 μmol/L) to inhibit these transporters was investigated. Acoramidis inhibited transport of substrates via P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K by 13.1%, 12.1%, 30.9%, 8.22%, 89.8%, 94.2%, 43.0%, and 21.9%, respectively. Acoramidis did not inhibit transport via OCT1, OCT2, or BSEP. To further understand inhibitory activity of acoramidis against OAT1, OAT3, and MATE1 in detail, the inhibitory activity of acoramidis at 0.3 to 100 μmol/L (1-200 μmol/L for MATE1) against transport of substrates of each of these transporters[22)] was investigated using MDCK-II cells expressing OAT1, OAT3, or MATE1, and IC_{50} was determined. The IC_{50} values of acoramidis against OAT1, OAT3, and MATE1 were 1.39, 1.26, and 178 μmol/L, respectively.

6.2.2 Studies in healthy adults

6.2.2.1 Single-dose and multiple-dose study in healthy non-Japanese adults (Study AG10-001, CTD 5.3.3.1-1, study period, August 2017 to February 2018)

A single dose of acoramidis 50, 150, 300, or 800 mg was administered orally to 42 healthy non-Japanese adults (n = 6/dose) in the fasted state, or acoramidis 100, 300, or 800 mg was administered orally to them in the fasted state twice daily for 12 days. Table 23 and Table 24 show PK parameters of acoramidis.

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20) Chemical compounds used as an inhibitor against each of the transporters are as follows: OAT3, probenecid (100 μmol/L); OCT1 and OCT2, quinidine (1000 μmol/L); OATP1B1 and OATP1B3, rifampicin (100 μmol/L); MATE1 and MATE2-K, cimetidine (100 μmol/L)

21) Chemical compounds used as a substrate of each of the transporters are as follows: P-gp, BCRP, and OATP1B3, cholecystokinin octapeptide (CCK-8) (0.1 μmol/L for P-gp, 1 μmol/L for BCRP, 2 μmol/L for OATP1B3); BSEP, taurocholate (1 μmol/L); OATP1B1, estradiol-17β-D-glucuronide (2 μmol/L); OAT1, p-aminohippuric acid (2 μmol/L); OAT3, estrone3-sulfate (100 μmol/L); OCT1, 1-methyl-4-phenylpyridinium (MPP^+) (2 μmol/L); OCT2, MATE1, and MATE2-K, metformin (10 μmol/L).

22) Chemical compounds used as a substrate of each of the transporters are as follows: OAT1, p-aminohippuric acid (2 μmol/L); OAT3, estrone3-sulfate (0.1 μmol/L); MATE1, metformin (10 μmol/L).

Table 23. PK parameters after single oral administration of acoramidis in the fasted state

Dose (mg)	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
50	6	2110 ± 210	0.8	28600 ± 3550	25.2 ± 2.9
150	6	3540 ± 1390	0.8	50600 ± 13700	27.6 ± 7.8
300	6	4510 ± 1050	0.8	52800 ± 18700 [b]	21.5 ± 5.9 [b]
800	6	11500 ± 3310	1.0	123000 ± 25700	27.5 ± 9.2

a Median; b, n = 5

Table 24. PK parameters after twice-daily multiple oral administration of acoramidis in the fasted state

Dose (mg)	Number of subjects	Measurement timepoint (Day)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
100	6	1	2630 ± 869	0.8	13600 ± 1750	-
	6	12	3590 ± 638	0.5	20600 ± 1810	23.5 ± 2.6
300	6	1	4500 ± 1820	0.8	19300 ± 3420	-
	6	12	7650 ± 3750	0.5	28700 ± 2650	29.8 ± 5.7
800	6	1	10200 ± 4780	1.1	35600 ± 6070	-
	6	12	13700 ± 6090	1.0	47200 ± 10300	28.8 ± 5.8

- Not calculated
a Median

6.2.2.2 Single-dose study in healthy non-Japanese adults (Study AG10-005, CTD 5.3.3.1-2, study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A single dose of acoramidis 1200, 1600, or 2000 mg was administered orally to 18 healthy non-Japanese adults (n = 6/dose) in the fasted state. Table 25 shows PK parameters of acoramidis.

Table 25. PK parameters after single oral administration of acoramidis in the fasted state

Dose (mg)	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
1200	6	9720 ± 4710	1.00	114000 ± 25400	19.6 ± 3.05
1600	6	17200 ± 3970	1.00	188000 ± 75900	26.5 ± 9.74
2000	6	18100 ± 9170	1.01	177000 ± 74500	22.0 ± 8.07

a Median

6.2.2.3 Single-dose study in healthy Japanese and non-Japanese adults (Study AG10-004, CTD 5.3.3.3-1, study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A single dose of acoramidis 400 or 800 mg was administered orally to 19 healthy Japanese and non-Japanese adults in the fasted state in a 2-treatment, 2-period, crossover manner (a 7-day washout period). Table 26 shows PK parameters of acoramidis.

Table 26. PK parameters after single oral administration of acoramidis in the fasted state

Dose (mg)	Target population	Number of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
400	Japanese	9	6621.1 ± 2342.7	1.0	106992.2 ± 33400.1	33.8 ± 12.5
	Non-Japanese	9	6521.1 ± 2119.7	1.0	100748.7 ± 24224.7	39.4 ± 18.1
800	Japanese	9	11698.9 ± 5766.9	1.0	177304.7 ± 83313.2	44.3 ± 27.8
	Non-Japanese	10	9640.0 ± 3871.4	1.0	182400.9 ± 90875.0	56.5 ± 34.3

a Median

6.2.2.4 Mass balance study (Study AG10-007, CTD 5.3.3.1-3 [reference data], study period [redacted] 20[redacted])

A single dose of ^{14}C-acoramidis 800 mg was administered orally to 6 healthy non-Japanese adults, and 68.0% and 34.4% of the radioactivity administered were excreted into urine and feces, respectively, by

216 hours post-dose. In the urine, acylglucuronate conjugate of acoramidis (30.8%) and unchanged acoramidis (7.9%) were mainly found. In the feces, unchanged acoramidis (15.39%) and oxidized form of acoramidis (9.24%) were mainly found.

6.2.3 Studies in patients

6.2.3.1 Foreign phase II study (Study AG10-201, CTD 5.3.5.1-1, study period, May to August 2018)

Acoramidis 400 or 800 mg was administered orally to 32 non-Japanese patients with wild-type ATTR-CM (ATTRwt-CM) or variant ATTR-CM (ATTRv-CM) (n = 16/dose) twice daily for 28 days. Table 27 and Table 28 show plasma acoramidis concentrations and TTR stabilization rate,[5)] respectively.

Table 27. Plasma acoramidis concentrations (ng/mL) on Day 28 of multiple oral administration of acoramidis

Dose (mg)	Pre-dose	0.5 hours post-dose	1 hour post-dose	2 hours post-dose
400	1841.3 ± 487.88 (16)	6455.0 ± 5984.35 (16)	6204.4 ± 2860.43 (16)	3905.0 ± 1050.16 (16)
800	2439.4 ± 900.08 (16)	11753.1 ± 7072.61 (16)	15640.6 ± 10638.76 (16)	9325.6 ± 7148.66 (16)

Mean ± SD (number of subjects)

Table 28. TTR stabilization rate (%) on Day 28 of multiple oral administration of acoramidis

		Pre-dose	0.5 hours post-dose	1 hour post-dose	2 hours post-dose
Placebo		-1.80 [-61.50, 23.40] (17)	0.95 [-70.70, 23.40] (16)	0.20 [-77.30, 14.70] (17)	0.20 [-63.20, 13.60] (17)
Acoramidis	400 mg	95.60 [50.20, 134.50] (16)	100.75 [69.00, 121.40] (16)	101.65 [68.00, 140.50] (16)	99.90 [69.10, 131.60] (16)
	800 mg	92.90 [64.10, 106.50] (16)	97.35 [73.50, 108.40] (16)	98.15 [65.70, 106.60] (16)	97.80 [66.20, 110.10] (15)

Median [minimum, maximum] (number of subjects)

6.2.3.2 Foreign phase III study (Study AG10-301, CTD 5.3.5.1-2, study period, April 2019 to May 2023)

Acoramidis 800 mg was administered orally to non-Japanese patients with ATTRwt-CM or ATTRv-CM twice daily. Table 29 and Table 30 show plasma acoramidis concentrations and TTR stabilization rate,[5)] respectively.

Table 29. Plasma acoramidis concentrations (ng/mL) following multiple oral administration of acoramidis

Day 28 (pre-dose)	Day 28 (1 hour post-dose)	Month 3 (pre-dose)	Month 12 (pre-dose)	Month 24 (pre-dose)	Month 30 (pre-dose)
2768.7 ± 1626.08 (120)	11028.1 ± 7277.64 (122)	2893.6 ± 1764.02 (115)	2594.9 ± 1134.40 (97)	2675.1 ± 1721.43 (93)	2358.0 ± 870.41 (94)

Mean ± SD (number of subjects)

Table 30. TTR stabilization rate (%) following multiple oral administration of acoramidis

	Day 28 (pre-dose)	Day 28 (1 hour post-dose)	Month 3 (pre-dose)	Month 12 (pre-dose)	Month 24 (pre-dose)	Month 30 (pre-dose)
Placebo	-2.200 [-85.74, 50.19] (49)	-3.723 [-97.45, 53.39] (49)	-2.752 [-335.42, 81.67] (49)	5.031 [-363.82, 50.33] (39)	11.766 [-384.55, 108.00] (35)	9.191 [-455.67, 87.84] (29)
Acoramidis	96.513 [4.34, 374.27] (110)	100.654 [75.21, 285.94] (108)	97.621 [-12.48, 263.94] (103)	95.643 [-10.05, 166.85] (83)	95.041 [-6.19, 150.24] (85)	97.636 [29.72, 194.49] (81)

Median [minimum, maximum] (number of subjects)

6.2.3.3 Japanese phase III study (Study ALXN2060-TAC-302, CTD 5.3.5.2-1, ongoing since November 2020, data cut-off on [redacted], 20[redacted])

Acoramidis 800 mg was administered orally to Japanese patients with ATTRwt-CM or ATTRv-CM twice daily. Table 31 and Table 32 show plasma acoramidis concentrations and TTR stabilization rate,[5)] respectively.

Table 31. Plasma acoramidis concentrations (ng/mL) following multiple oral administration of acoramidis

Day 28 (pre-dose)	Day 28 (1 hour post-dose)	Month 3 (pre-dose)	Month 12 (pre-dose)	Month 24 (pre-dose)	Month 30 (pre-dose)
2759.0 ± 1448.80 (24)	11005.8 ± 8437.22 (24)	2730.8 ± 1117.63 (24)	2535.0 ± 1049.28 (22)	2339.5 ± 669.69 (21)	2535.2 ± 1007.82 (21)

Mean ± SD (number of subjects)

Table 32. TTR stabilization rate (%) following multiple oral administration of acoramidis

Day 28 (pre-dose)	Month 3 (pre-dose)	Month 12 (pre-dose)	Month 24 (pre-dose)	Month 30 (pre-dose)
97.29 [-526.7, 117.1] (24)	99.09 [-777.3, 105.2] (24)	100.89 [-533.6, 106.9] (22)	102.60 [-625.6, 109.9] (22)	95.60 [-1701.2, 108.2] (21)

Median [minimum, maximum] (number of subjects)

6.2.4 Studies for drug-interactions

6.2.4.1 Study for drug-interactions with adefovir and oseltamivir (Study AG10-008, CTD 5.3.3.4-1 [reference data], study period, [redacted] to [redacted] 20[redacted])

The study included 32 healthy non-Japanese adults and consisted of Part 1 and Part 2, each consisting of Period 1 and Period 2. In Period 1 of Part 1 (n = 14), a single dose of adefovir 10 mg was administered orally, and in Period 2, acoramidis 800 mg was administered orally twice daily for 8 days, starting 6 days before the single dose of adefovir 10 mg (drug-free period of 1 day). In Period 1 of Part 2 (n = 18), a single dose of oseltamivir 75 mg was administered orally, and in Period 2, acoramidis 800 mg was administered orally twice daily for 9 days, starting 6 days before the single dose of oseltamivir 75 mg (drug-free period of 2 days). The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of adefovir after co-administration of adefovir and acoramidis to those after administration of adefovir alone were 0.9227 [0.8351, 1.0194] and 1.1863 [1.1030, 1.2759], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of oseltamivir carboxylate after co-administration of oseltamivir and acoramidis to those after administration of oseltamivir alone were 0.9323 [0.8832, 0.9842] and 1.0352 [0.9944, 1.0778], respectively.

6.2.5 PPK analysis (Analysis ALEX-PMX-ALXN2060-5508, CTD 5.3.3.5-3)

A population pharmacokinetic (PPK) analysis (NONMEM Version 7.4.3) was performed using data on plasma acoramidis concentrations at 4645 sampling points from 330 subjects, who were included in the foreign phase I studies (Studies AG10-001, AG10-003, AG10-004, AG10-005, and ALXN2060-HV-101) in healthy adults, foreign phase II studies (Studies AG10-201 and AG10-202), foreign phase III study (Study AG10-301), and Japanese phase III study (Study ALXN2060-TAC-302) in patients with ATTR-CM.

The characteristics of subjects included in the analysis were age of 70.1 [18.0, 89.3] years (median [minimum, maximum]), body weight of 77.5 [43.8, 133] kg, creatinine clearance (CrCL) of 75.1 [25.9, 190] mL/min, estimated glomerular filtration rate (eGFR) of 74.6 [25.4, 157] mL/min/1.73 m^2, and a dose of 800 [50, 2000] mg. The PPK analysis population as follows: Sex, 269 males and 61 females; race, 229 whites, 43 blacks or African Americans, 5 non-Japanese Asians, 33 Japanese, 17 individuals of other ethnic groups, and 3 of unknown ethnic groups; health status, 121 healthy adults and 209 patients with ATTR-CM; concomitant use of diuretics, 158 individuals not concomitantly using diuretics and 172 concomitantly using diuretics; and timing of acoramidis use, 112 individuals receiving acoramidis in the fasted state, 9 in the fed state, and 209 in unknown states.

In this analysis, a model[23)] established by the PPK analysis using data from 8 clinical studies except for Study ALXN2060-TAC-302 was used as the base model to search for additional covariates from candidates of age, body weight, sex, ethnic group, CrCL, eGFR, health status, and concomitant use of diuretics for PK parameters (CL/F, V_c/F, and K_a). The health status (patients with ATTR-CM or healthy adults) for CL/F and V_c/F as well as CrCL (baseline) and ethnic group (white, Japanese, or other groups) for CL/F were added as covariates.

Population mean estimates of the parameters in the final model (relative standard error [RSE]) were 2.60 L/h (1.65%) for CL/F, 5.52 L (4.17%) for V_c/F, 5.76 L/h (0.565%) for Q/F, 31.7 L (6.16%) for V_p/F, 11.2 h^{-1} (1.01%) for K_a, and 0.565 h (2.22%) for D1. Estimates of inter-individual variability (RSE) were 12.5% (19.4%) for CL/F, 26.3% (14.3%) for V_c/F, 14.9% (26.2%) for V_p/F, and 334% (1.49%) for K_a.

Using individual parameter estimates obtained from the final model, PK parameters of acoramidis in non-Japanese patients in Study AG10-301 and Japanese patients in Study ALXN2060-TAC-302 who received acoramidis 800 mg twice daily were estimated. Table 33 shows the PK parameter estimates.

Table 33. PK parameter estimates of acoramidis in patients in Studies AG10-301 and ALXN2060-TAC-302

Target population	Number of subjects	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng·h/mL)
Non-Japanese patients (Study AG10-301)	136	2821 ± 1175	15438 ± 2206	57416 ± 15579
Japanese patients (Study ALXN2060-TAC-302)	24	2638 ± 1429	15768 ± 1650	55486 ± 18761

[23)] It was described as a 2-compartment model with sequential zero-order and first-order absorption, and dose effect for relative bioavailability (BA) and food effect for absorption parameters (K_a and D1) were included as covariates.

6.2.6 Relationship between exposure and change in QT/QTc interval (CTD 5.3.3.1-2)

Based on data from foreign phase I studies (Studies AG10-001 and AG10-005), a relationship between plasma acoramidis concentrations and ΔΔQTcF was investigated using a linear mixed effects model. With increasing plasma acoramidis concentrations, ΔΔQTcF tended to shorten, and the upper limit of 90% CI of ΔQTcF was estimated to be below 10 milliseconds within a range of plasma acoramidis concentrations resulting from its use according to the studied regimens.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK and PD of acoramidis between Japanese and non-Japanese subjects

The applicant's explanation:

No differences were noted in PK or pharmacodynamics (PD) of acoramidis between Japanese and non-Japanese subjects in view of the following points:

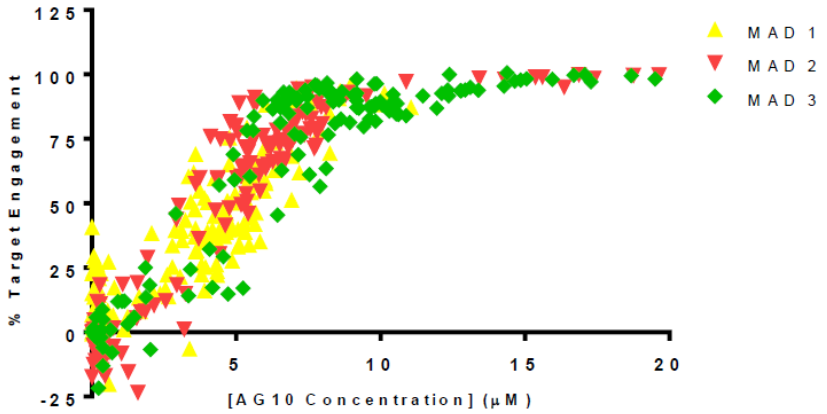
- In the phase I study in healthy Japanese and non-Japanese adults (Study AG10-004) and the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) in patients with ATTR-CM, no clear differences were observed in plasma acoramidis concentrations or PK parameters after a single-dose or multiple-dose administration of acoramidis between Japanese and non-Japanese subjects. No clear differences were also observed in PK parameter estimates of acoramidis obtained in the final model for the PPK analysis between Japanese and non-Japanese subjects [see Sections "6.2.2.3 Single-dose study in healthy Japanese and non-Japanese adults," "6.2.3.2 Foreign phase III study," "6.2.3.3 Japanese phase III study," and "6.2.5 PPK analysis"].
- In Studies AG10-301 and ALXN2060-TAC-302, the TTR stabilization rate (median) in patients with ATTR-CM at steady state reached by multiple doses achieved an almost perfect score in both Japanese and non-Japanese patients [see Sections "6.2.3.2 Foreign phase III study" and "6.2.3.3 Japanese phase III study"].

In view of the submitted data, PMDA concluded that no clear differences are observed in PK or PD of acoramidis between Japanese and non-Japanese subjects.

6.R.2 Appropriateness of proposed dosage and administration

The applicant's explanation about rationale for the dosage regimen in the Japanese phase III study (Study ALXN2060-TAC-302) and appropriateness of the proposed dosage and administration from viewpoints of PK and PD:

In the phase I study in healthy non-Japanese adults (Study AG10-001), acoramidis 100, 300, or 800 mg was administered orally twice daily for 12 days. Figure 1 shows a relationship between trough plasma acoramidis concentrations on Day 12 and TTR stabilization rates. Based on this figure, the trough plasma acoramidis concentration of 2340 ng/mL (approximately 8 μM) was established as the target value that requires almost perfect TTR stabilization (≥90%).



Horizontal axis, Trough plasma acoramidis concentration (μM) on Day 12; Vertical axis, TTR stabilization rate on Day 12 (%, measured by the FPE method); Multiple ascending dose (MAD)1, acoramidis 100 mg twice daily; MAD2, acoramidis 300 mg twice daily; MAD3, acoramidis 800 mg twice daily

Figure 1. Relationship between trough plasma acoramidis concentrations and TTR stabilization rates at steady state

In the phase I study in healthy non-Japanese adults (Study AG10-005), the mean plasma acoramidis concentration at 24 hours after the single-dose administration of acoramidis 1600 mg was 1660 ng/mL, and the accumulation ratio with multiple-dose administration was 1.3 to 1.6. In view of these results, on once-daily regimen of acoramidis 1600 mg, the trough plasma acoramidis concentration was not projected to reach the target value (2340 ng/mL), and thus the twice-daily regimen was selected for acoramidis in phase II and later phase clinical studies. In Study ALXN2060-TAC-302, the twice-daily regimen of acoramidis 800 mg was also selected as done in the foreign phase III study (Study AG10-301), because (1) in the foreign phase II study in patients with ATTR-CM (Study AG10-201), acoramidis 400 or 800 mg was administered orally twice daily for 28 days, and results below were obtained, and (2) in the phase I study in healthy Japanese and non-Japanese adults (Study AG10-004), the single oral administration of acoramidis did not raise clear differences in PK between Japanese and non-Japanese subjects.

- The trough plasma acoramidis concentration at steady state on the twice-daily regimen of acoramidis 800 mg exceeded the target value (mean, 2439.4 ng/mL; median, 2360.0 ng/mL), while on the twice-daily regimen of acoramidis 400 mg, the trough concentration did not reach the target value (mean, 1841.3 ng/mL; median, 1955.0 ng/mL).
- The twice-daily regimen of acoramidis 800 mg achieved a ≥50% increase in serum TTR in a larger proportion of patients (38%) than the twice-daily regimen of acoramidis 400 mg (19%).
- Safety profile with the twice-daily regimen of acoramidis 800 mg was similar to that with the twice-daily regimen of acoramidis 400 mg.

Taking into account that no clear differences were observed in PK or PD between Japanese and non-Japanese subjects in Studies ALXN2060-TAC-302 and AG10-301 which were conducted with the twice-daily regimen of acoramidis 800 mg [see Section "6.R.1 Differences in PK and PD of acoramidis between Japanese and non-Japanese subjects"], the concerned regimen may be used as the proposed dosage and administration with justification.

In view of the applicant's explanation and from viewpoints of PK and PD, PMDA accepted the dosage regimen selected for Study ALXN2060-TAC-302 and the proposed dosage and administration that reflect the regimen used in Study ALXN2060-TAC-302.

6.R.3 Use in patients with hepatic impairment

The applicant's explanation about use of acoramidis in patients with hepatic impairment:
Patients with cardiac failure and hepatic impairment concurrently had poor outcomes (*JACC Heart Fail.* 2019;7:87-97, *Rev Cardiovasc Med.* 2021;22:925-9), and patients with ATTR-CM and hepatic impairment concurrently were presumed to be very limited. Patients with abnormal liver function test values at screening (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 times the upper limit of normal [ULN] or total bilirubin >3 times the ULN) were excluded from the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) of acoramidis in patients with ATTR-CM.

To examine eligibility of patients with hepatic impairment for acoramidis, a comparison of incidences of adverse events was performed between the subgroup with all baseline liver function test values (ALT, AST, and total bilirubin) at or below the ULN and subgroup with any of the liver function test values above the ULN in Studies AG10-301 and ALXN2060-TAC-302. Because no marked difference was observed in incidence of adverse events between the subgroups (Table 34), acoramidis does not have to be contraindicated for patients with hepatic impairment. Yet, acoramidis is excreted into bile, and caution will be raised in the package insert about (1) possible increase in plasma acoramidis concentrations in patients with hepatic impairment; and (2) the exclusion of patients with abnormal liver function test values from the clinical studies.

Table 34. Incidences of adverse events by liver function test values at baseline (at or below the ULN or above the ULN) in Studies AG10-301 and ALXN2060-TAC-302 (safety analysis set)

	All liver function test values[a] at baseline at or below the ULN			Any of liver function test values[a] at baseline above the ULN		
	Study AG10-301		Study ALXN2060-TAC-302 (n = 20)	Study AG10-301		Study ALXN2060-TAC-302 (n = 5)
	Placebo (n = 134)	Acoramidis (n = 255)		Placebo (n = 77)	Acoramidis (n = 166)	
All adverse events	97.0 (130)	97.3 (248)	100 (20)	98.7 (76)	99.4 (165)	100 (5)
Serious adverse events	60.4 (81)	53.3 (136)	50.0 (10)	72.7 (56)	56.6 (94)	40.0 (2)
Adverse events leading to death	13.4 (18)	12.2 (31)	0 (0)	23.4 (18)	17.5 (29)	0 (0)
Adverse events leading to discontinuation of the study drug	4.5 (6)	11.4 (29)	5.0 (1)	15.6 (12)	6.0 (10)	20.0 (1)
Adverse events for which a causal relationship to the study drug could not be ruled out	5.2 (7)	11.8 (30)	10.0 (2)	5.2 (4)	12.0 (20)	20.0 (1)

Incidence (%) (number of subjects with events)
a ALT, AST, and total bilirubin

PMDA's view:
In view of the elimination of acoramidis from the body, to which metabolism in the liver and biliary excretion contribute, plasma acoramidis concentrations may increase in patients with hepatic

impairment, but to what extent plasma acoramidis concentrations would be varied according to presence or absence of hepatic impairment and its severity remains unclear, because no clinical pharmacology studies have been conducted. In addition to the points below, however, ATTR-CM is a serious disease with a poor prognosis, and addition of the new option to treatment of ATTR-CM, for which only tafamidis meglumine and tafamidis (tafamidis) is approved in Japan, is considered meaningful.

- In the foreign phase I study (Study AG10-005) with a single oral administration of acoramidis 1200, 1600, or 2000 mg and foreign phase II study (Study AG10-201) with twice-daily oral regimen of acoramidis 400 or 800 mg, incidence of adverse events did not tend to increase with the dose, and a risk dependent on plasma acoramidis concentrations was not suggested [see Section "7.2.1 Foreign phase II study"].
- No remarkable difference was noted in incidence of adverse events between the subgroups of patients with all of the liver function test values (ALT, AST, and total bilirubin) at or below the ULN and those with any of the liver function test values above the ULN in either foreign or Japanese phase III study (Table 34).

Based on the above findings, patients with hepatic impairment may be deemed eligible for acoramidis, when cautions are raised in the package insert about possible increase in plasma acoramidis concentrations in patients with hepatic impairment and the exclusion of patients with abnormal liver function test values (ALT or AST >3 times the ULN or total bilirubin >3 times the ULN) from the clinical studies.

6.R.4 Concomitant use of acoramidis with substrates of CYP2C8 or CYP2C9

In view of results from *in vitro* studies for time-dependent inhibitory activity of acoramidis against CYP2C8 and CYP2C9 [see Section "6.2.1.4.1 Inhibition against CYP isoforms"], PMDA asked the applicant to explain a possibility for acoramidis to inhibit CYP2C8 and CYP2C9 when used according to the recommended clinical dose and necessity of raising caution for concomitant use of acoramidis with substrates of CYP2C8 or CYP2C9.

The applicant's explanation:

No clinical studies for drug interactions of acoramidis with substrates of CYP2C8 or CYP2C9 have been conducted, and thus adverse events in patients who received substrates[24)] of CYP2C8 or CYP2C9 concomitantly in the foreign phase III study (Study AG10-301) were evaluated to determine whether raising caution for concomitant use of acoramidis with substrates of CYP2C8 or CYP2C9 is necessary.

Table 35 shows substrates of CYP2C8 or CYP2C9 permitted to be concomitantly used with the study drug in both placebo and acoramidis groups in Study AG10-301.

[24)] The following are the selected (a) substrates of CYP2C8 or CYP2C9 for which concomitant use is contraindicated or cautioned in the package inserts of the drugs approved in Japan that are assumed to require dose adjustment due to their inhibitory activity against CYP2C8 or CYP2C9 or (b) drugs that are reported to be substrates of CYP2C8 or CYP2C9 (*Drug Metabolism and Pharmacokinetics.* 2021;41:100414).
Substrates of CYP2C8: Apalutamide, bexarotene, dabrafenib, daprodustat, enzalutamide, iptacopan, paclitaxel, pemafibrate, repaglinide, roxadustat, selexipag, treprostinil, montelukast, pioglitazone
Substrates of CYP2C9: Bosentan, celecoxib, glimepiride, macitentan, phenytoin, ramelteon, siponimod, warfarin, tolbutamide

Table 35. Substrates of CYP2C8 or CYP2C9 permitted to be concomitantly used with the study drug in both placebo and acoramidis groups in Study AG10-301

Substrate	Drug	Placebo (n = 211)	Acoramidis (n = 421)
CYP2C8 substrate	Montelukast	1.4 (3)	1.0 (4)
CYP2C9 substrate	Warfarin	15.2 (32)	9.7 (41)
	Celecoxib	1.4 (3)	1.2 (5)
	Glimepiride	1.4 (3)	1.0 (4)

% (number of subjects)

A check for adverse events[25)] potentially related to adverse drug reactions of montelukast, a CYP2C8 substrate, in patients treated concomitantly with montelukast, revealed that diarrhoea and cough occurred in 1 patient each in the acoramidis group, but the incidence did not tend to increase with concomitant use of acoramidis.

Adverse events in patients treated concomitantly with a drug potentially acting as a CYP2C9 substrate were investigated as described below. Table 36 shows incidence of adverse events[26)] with bleeding, an adverse drug reaction of warfarin, occurred in patients treated concomitantly with warfarin. International normalised ratio increased occurred in 8 patients only in the acoramidis group, but the incidence of adverse events with bleeding did not tend to increase with concomitant use of acoramidis. A check for incidences of adverse events[27)] potentially related to adverse drug reactions of celecoxib in patients treated concomitantly with celecoxib revealed that constipation occurred in 1 patient in the placebo group, and abdominal pain upper occurred in 2 patients, and constipation, nausea, abdominal pain, gastrooesophageal reflux disease, inguinal hernia, abdominal discomfort, anal incontinence, abdominal pain lower, abdominal hernia, gastritis erosive, gastrointestinal pain, and umbilical hernia occurred in 1 patient each in the acoramidis group, but the incidence did not tend to increase with concomitant use of acoramidis. A check for incidences of adverse events[28)] potentially related to adverse drug reactions of glimepiride in patients treated concomitantly with glimepiride revealed that diarrhoea, abdominal discomfort, and diverticulum intestinal haemorrhagic occurred in 1 patient each in the placebo group; and diarrhoea, inguinal hernia, intestinal obstruction, and hypoglycaemia occurred in 1 patient each in the acoramidis group, but the incidence did not tend to increase with concomitant use of acoramidis.

25) Medical Dictionary for Regulatory Activities (MedDRA) Preferred terms (PT) “Upper respiratory tract infection,” “Pyrexia,” “Headache,” “Pharyngitis,” “Cough,” “Abdominal pain,” and “Diarrhoea”
26) Standardised MedDRA queries (SMQ) “Haemorrhages” [broad] as well as MedDRA PT “Cardiac tamponade,” “International normalised ratio fluctuation,” “Faecal occult blood,” and “Anaemia”
27) MedDRA System organ class (SOC) “Gastrointestinal disorders”
28) MedDRA SMQ “Hypoglycaemia” [narrow], MedDRA SMQ “Hyperglycaemia/new onset diabetes mellitus” [narrow] and MedDRA SOC “Gastrointestinal disorders”

Table 36. Incidences of adverse events with bleeding in patients treated concomitantly with warfarin in Study AG10-301 (safety analysis set)

MedDRA PT	Placebo (n = 32)	Acoramidis (n = 41)
International normalised ratio increased	0 (0)	19.5 (8)
Haematuria	9.4 (3)	7.3 (3)
Epistaxis	6.3 (2)	4.9 (2)
Anaemia	12.5 (4)	2.4 (1)
Gingival bleeding	0 (0)	2.4 (1)
Haemorrhoidal haemorrhage	0 (0)	2.4 (1)
Subarachnoid haemorrhage	0 (0)	2.4 (1)
Haemoptysis	0 (0)	2.4 (1)
Faecal occult blood positive	0 (0)	2.4 (1)
International normalised ratio fluctuation	0 (0)	2.4 (1)
Skin haemorrhage	0 (0)	2.4 (1)
Blood loss anaemia	0 (0)	2.4 (1)
Contusion	9.4 (3)	0 (0)
Cardiac tamponade	3.1 (1)	0 (0)
Large intestinal haemorrhage	3.1 (1)	0 (0)
Oral blood blister	3.1 (1)	0 (0)
Tongue haematoma	3.1 (1)	0 (0)
Tongue haemorrhage	3.1 (1)	0 (0)
Post procedural haemorrhage	3.1 (1)	0 (0)
Traumatic haemothorax	3.1 (1)	0 (0)
Faecal occult blood	3.1 (1)	0 (0)
Haematoma	3.1 (1)	0 (0)
Varicose vein ruptured	3.1 (1)	0 (0)
Coagulopathy	3.1 (1)	0 (0)
Retinal haemorrhage	3.1 (1)	0 (0)

Incidence % (number of subjects)

As shown above, evaluation in patients receiving acoramidis concomitantly with a substrate of CYP2C8 or CYP2C9 has limitations because of the small sample size, but no safety concerns are noted for concomitant use of acoramidis with a substrate of CYP2C8 or CYP2C9. Acoramidis is, therefore, unlikely to affect PK of a substrate of CYP2C8 or CYP2C9. The applicant intends to inform that acoramidis inhibited CYP2C8 and CYP2C9 *in vitro* via the package insert but considers it unnecessary to raise further caution.

PMDA's view:

A substrate of CYP2C8 concomitantly used with acoramidis in Study AG10-301 was only montelukast, and limited number of patients received it. In view of the incidences of adverse events potentially related to adverse drug reactions of montelukast in the study, cautionary advice on concomitant use of acoramidis with substrates of CYP2C8 is unnecessary at present. Warfarin is a typical substrate of CYP2C9 and has a relatively narrow safety margin. The inhibitory effect of acoramidis against CYP2C9 can be investigated based on data in patients receiving acoramidis and concomitant warfarin in the study. In view of the incidences of adverse events accompanied by bleeding in the study, cautionary advice on concomitant use of acoramidis with substrates of CYP2C9 is unnecessary at present.

Taken together, the applicant's actions are considered reasonable. However, in view of limited investigations in Study AG10-301 and undeniable possibility of clinically relevant PK interactions in the future, information about drug interactions between acoramidis and substrates of CYP2C8 or CYP2C9 should be further collected in the post-marketing setting.

6.R.5 Inhibitory activity of acoramidis against P-gp, BCRP, OATP1B1, OATP1B3, and MATE2-K

In the *in vitro* study, a potential of acoramidis to inhibit P-gp, BCRP, OATP1B1, OATP1B3, and MATE2-K was investigated, but the concentration of acoramidis investigated was only 30 μmol/L, at which inhibitory activity against these transporters was observed. In view of the finding, PMDA asked the applicant to explain a possibility of acoramidis causing PK interactions via inhibitory activity against these transporters.

The applicant's explanation:

In view of *in vitro* study results obtained after submission of the present application shown below, estimated plasma concentrations of unbound acoramidis[29)] after administration of acoramidis according to the recommended clinical dosage regimen, and the incidences of adverse events in the clinical studies, inhibitory activity of acoramidis against P-gp, BCRP, OATP1B1, OATP1B3, and MATE2-K is unlikely to pose clinical problems.

- Using MDCK-II cells expressing P-gp, OATP1B3, or MATE2-K, a potential of acoramidis (3-1000 μmol/L for P-gp, 1-200 μmol/L for OATP1B3, 0.3-100 μmol/L for MATE2-K) to inhibit transport of substrates[30)] of each of these transporters was investigated. The IC_{50} values of acoramidis against P-gp, OATP1B3, and MATE2-K were >1000 μmol/L, 125 μmol/L, and >100 μmol/L, respectively.
- Using MDCK-II cells expressing BCRP, a potential of acoramidis (3-1000 μmol/L) to inhibit transport of a substrate of BCRP (prazosin 2 μmol/L) was investigated. The IC_{50} of acoramidis against BCRP was 440 μmol/L, but the solubility of acoramidis at pH 6.0 to 6.8, which is assumed to reflect a condition in the gastrointestinal tract, is <1.40 mg/mL.
- Using MDCK-II cells expressing OATP1B1, a potential of acoramidis (1-200 μmol/L) to inhibit transport of a substrate of OATP1B1 (estradiol-17β-D-glucuronide 2 μmol/L) was investigated. The IC_{50} of acoramidis against OATP1B1 was 55.5 μmol/L, and thus acoramidis was considered to potentially inhibit OATP1B1 when used according to the recommended clinical dosage regimen. No clinical studies for drug interactions of acoramidis with substrates of OATP1B1 are conducted, and thus adverse events in patients who received substrates[31)] of OATP1B1 concomitantly in the foreign phase III study (Study AG10-301) were evaluated to determine whether raising caution for concomitant use of acoramidis with substrates of OATP1B1 is necessary. Substrates of OATP1B1 concomitantly used with the study drug in both placebo and acoramidis groups in Study AG10-301 were hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors,[32)] and 56.9% (120 of 211) of patients in the placebo group and 60.1% (253 of 421) of patients in the acoramidis group received these drugs concomitantly. Table 37 shows incidences of adverse events[33)] potentially related to adverse drug reactions of HMG-CoA reductase inhibitors in patients treated concomitantly with HMG-CoA reductase inhibitors. The incidence did not tend to increase with concomitant use of

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29) It was estimated to be 1.69 μmol/L from the C_{max} (13700 ng/mL) and unbound fraction in plasma (0.036) projected with administration of acoramidis according to the recommended clinical dosage regimen.

30) Chemical compounds used as a substrate of each of the transporters are as follows: P-gp, quinidine (0.1 μmol/L); OATP1B3, CCK-8 (2 μmol/L); MATE2-K, metformin (10 μmol/L)

31) Based on drugs reported as substrates of OATP1B1 (*Drug Metabolism and Pharmacokinetics.* 2021;41:100414), asunaprevir, atorvastatin, bosentan, docetaxel, glibenclamide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, and simvastatin were selected.

32) Atorvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin

33) MedDRA PT "Myalgia," "Musculoskeletal chest pain," "Muscular weakness," "Musculoskeletal pain," "Muscular atrophy," "Musculoskeletal stiffness," "Rhabdomyolysis," "Muscle fatigue," "Musculoskeletal discomfort," and "Myositis"

acoramidis, and thus acoramidis is unlikely to affect PK of substrates of OATP1B1. The package insert will note that acoramidis inhibits OATP1B1 *in vitro*, but further cautionary advice is unnecessary.

Table 37. Incidences of adverse events potentially related to adverse drug reactions of HMG-CoA reductase inhibitors in patients treated concomitantly with HMG-CoA reductase inhibitors in Study AG10-301 (safety analysis set)

MedDRA PT	Placebo (n = 120)	Acoramidis (n = 253)
Myalgia	5.8 (7)	2.4 (6)
Musculoskeletal chest pain	0.8 (1)	2.4 (6)
Muscular weakness	0 (0)	1.2 (3)
Musculoskeletal pain	0 (0)	1.2 (3)
Musculoskeletal stiffness	0 (0)	0.8 (2)
Rhabdomyolysis	0.8 (1)	0.4 (1)
Muscle fatigue	0 (0)	0.4 (1)
Myositis	0 (0)	0.4 (1)
Muscular atrophy	1.7 (2)	0 (0)
Musculoskeletal discomfort	0.8 (1)	0 (0)

Incidence % (number of subjects)

PMDA's view:

In view of *in vitro* study results obtained after submission of the present application, the applicant's explanation that inhibitory activity of acoramidis against P-gp, BCRP, OATP1B3, and MATE2-K is unlikely to pose clinical problems is acceptable. In view of *in vitro* study results of inhibitory activity of acoramidis against OATP1B1, on the other hand, acoramidis was considered to potentially inhibit OATP1B1 when used according to the recommended clinical dosage regimen. HMG-CoA reductase inhibitors are typical substrates of OATP1B1, and a certain number of patients received these drugs concomitantly in Study AG10-301. An effect of inhibitory activity of acoramidis against OATP1B1 can be investigated based on data in patients receiving acoramidis concomitantly with HMG-CoA reductase inhibitors in Study AG10-301. PMDA considers it unnecessary to raise caution about concomitant use of acoramidis with substrates of OATP1B1 at present.

As shown above, PMDA considers the applicant's actions appropriate, but the investigations in Study AG10-301 are limited, and a possibility of clinically relevant PK interactions being found in the future cannot be ruled out. The applicant is thus required to continue collecting information about drug interactions of acoramidis with substrates of OATP1B1 even after the market launch.

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

The applicant submitted main efficacy and safety evaluation data, in the form of results from 5 studies shown in Table 38 [for PK and PD, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"]. In this section, doses of acoramidis are expressed as the amounts of acoramidis hydrochloride.

Table 38. Main efficacy and safety evaluation data

Data category	Region	Study	Phase	Population	Number of subjects enrolled	Regimen	Main endpoints
Evaluation	Foreign	AG10-001	I	Healthy adults	Part A: 32 Part B: 24	Part A: Single oral administration of placebo, acoramidis 50, 150, 300, or 800 mg Part B: Oral twice-daily administration of placebo, acoramidis 100, 300, or 800 mg for 12 days	Safety PK/PD
	Foreign	AG10-004	I	Healthy adults	19	Single oral administration of acoramidis 400 or 800 mg in Period 1 followed by washout period of 7 days, and then single oral administration of acoramidis 800 or 400 mg in Period 2	Safety PK
	Foreign	AG10-201	II	Patients with ATTRwt-CM or ATTRv-CM	49	Oral twice-daily administration of placebo, acoramidis 400 or 800 mg for 28 days	Safety PK/PD
	Foreign	AG10-301	III	Patients with ATTRwt-CM or ATTRv-CM	632	Oral twice-daily administration of placebo or acoramidis 800 mg for 30 months	Efficacy Safety
	Japan	ALXN2060-TAC-302	III	Patients with ATTRwt-CM or ATTRv-CM	25	Oral twice-daily administration of acoramidis 800 mg for 30 months (open-label treatment period)	Efficacy Safety PK/PD

7.1 Phase I studies

7.1.1 Phase I study in healthy non-Japanese adults (Study AG10-001, CTD 5.3.3.1-1, study period, August 2017 to February 2018)

A randomized, double-blind study was conducted at a single study center in the US to evaluate safety, PK, and PD of acoramidis in healthy non-Japanese adults who orally received acoramidis as a single dose or multiple doses (target sample size, 32 subjects in Part A [2 in the placebo group and 6 in the acoramidis group/cohort], 24 subjects in Part B [2 in the placebo group and 6 in the acoramidis group/cohort]).

In this study consisting of Part A and B, subjects were randomized to receive placebo or acoramidis in a 1:3 ratio for each cohort.

Table 39 shows the dosage regimens. In Cohort 3 of Part A, subjects received placebo or acoramidis in the fasted state in Period 1 and in the fed state in Period 2 in a 2-treatment, 2-period, crossover manner (a ≥14-day washout period).

Table 39. Dosage regimen for each cohort in Parts A and B

	Cohort	Dosage regimen
Part A	1	Single oral administration of placebo or acoramidis 50 mg in the fasted state
	2	Single oral administration of placebo or acoramidis 150 mg in the fasted state
	3	Single oral administration of placebo or acoramidis 300 mg in the fasted or fed state
	4	Single oral administration of placebo or acoramidis 800 mg in the fasted state
Part B	1	Oral twice-daily administration of placebo or acoramidis 100 mg for 12 days
	2	Oral twice-daily administration of placebo or acoramidis 300 mg for 12 days
	3	Oral twice-daily administration of placebo or acoramidis 800 mg for 12 days

A total of 56 randomized subjects (32 in Part A [8 in the placebo group, 24 in the acoramidis group] and 24 in Part B [6 in the placebo group, 18 in the acoramidis group]) received the study drug and all were included in the safety analysis set. None discontinued the study.

In Part A, adverse events occurred in 25.0% (2 of 8) of subjects in the pooled placebo group (pool of the placebo group in each cohort), 50.0% (3 of 6) of subjects in the acoramidis 50 mg group, 33.3% (2 of 6) of subjects in the acoramidis 150 mg group, 0% (0 of 6) of subjects in the acoramidis 300 mg in the fasted state group, 16.7% (1 of 6) of subjects in the acoramidis 300 mg in the fed state group, and 16.7% (1 of 6) of subjects in the acoramidis 800 mg group, and there were no adverse events that occurred in ≥2 subjects in any group. In Part B, adverse events occurred in 50.0% (3 of 6) of subjects in the pooled placebo group, 33.3% (2 of 6) of subjects in the acoramidis 100 mg group, 83.3% (5 of 6) of subjects in the acoramidis 300 mg group, and 16.7% (1 of 6) of subjects in the acoramidis 800 mg group, and an adverse event that occurred in ≥2 subjects in any group was limited to upper respiratory tract infection in 2 subjects in the acoramidis 300 mg group.

In both Part A and B, no adverse events leading to death, serious adverse events, or adverse events leading to discontinuation of the study drug occurred.

7.1.2 Phase I study in healthy Japanese and non-Japanese adults (Study AG10-004, CTD 5.3.3.3-1, study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, open-label, 2-treatment, 2-period, crossover study was conducted at a single study center in the US to evaluate safety and PK of acoramidis in healthy Japanese and non-Japanese adults who orally received a single dose of acoramidis (target sample size, 20 subjects [10 each of Japanese and non-Japanese subjects]).

In Period 1, a single dose of acoramidis 400 or 800 mg was administered orally, and in Period 2, a single dose of acoramidis 800 or 400 mg was administered orally (a 7-day washout period).

A total of 19 randomized subjects (9 Japanese and 10 non-Japanese) received the study drug and all were included in the safety analysis set. One non-Japanese subject discontinued the study because of an adverse event.[34)]

At doses of 400 mg and 800 mg of acoramidis, adverse events occurred in 0% (0 of 9) and 11.1% (1 of 9) (dizziness) of Japanese subjects, respectively, and 11.1% (1 of 9) (tinnitus and visual field defect) and 20.0% (2 of 10) (nausea and upper respiratory tract infection; and muscle strain in 1 subject each) of non-Japanese subjects, respectively.

No adverse events leading to death, serious adverse events, or adverse events leading to discontinuation of the study drug occurred.

[34)] The subject experienced muscle strain after receiving acoramidis 800 mg in Period 1 and discontinued the study without receiving the treatment in Period 2.

7.2 Phase II study

7.2.1 Foreign phase II study (Study AG10-201, CTD 5.3.5.1-1, study period, May to August 2018)

A placebo-controlled, randomized, double-blind study was conducted at 9 study centers outside Japan to evaluate safety, PK, and PD of acoramidis in patients with ATTRwt-CM or ATTRv-CM (target sample size, approximately 55 subjects [approximately 18 per group]).

This study consisted of a screening period up to 28 days, a double-blind treatment period of 28 days, and a follow-up period of 7 to 14 days.

In this study, patients with ATTR-CM[35] aged ≥18 and ≤90 years who had New York Heart Association (NYHA) Class II or III symptoms and met the criteria below were mainly included.

- Patients who received a definitive diagnosis of ATTRwt-CM or ATTRv-CM confirmed by either of the following examinations and genotyping:
  (a) TTR amyloid deposition documented with endomyocardial biopsy specimen; or
  (b) Positive image documented by ^{99m} technetium (Tc) pyrophosphate scintigraphy.[36]
- Patients who have a history of cardiac failure meeting either of the following criteria:
  (a) Have a history of hospitalization due to cardiac failure; or
  (b) Have no history of hospitalization due to cardiac failure but have clinical evidence of cardiac failure requiring medical management (increased N-terminal prohormone of brain natriuretic peptide [NT-proBNP], use of diuretics, etc.).
- For patients taking cardiovascular medical therapy except for diuretics, those who had been on stable doses[37] for at least 2 weeks before screening

The main exclusion criteria are as follows:

- Patients who are found to have abnormal liver function test values[38] at screening
- Patients who have eGFR <30 mL/min/1.73 m^2 at screening

In this study, placebo or acoramidis 400 or 800 mg was administered orally twice daily for 28 days.

Tafamidis, diflunisal, doxycycline hydrochloride hydrate, green tea extract, tauroursodeoxycholic acid, ursodeoxycholic acid, patisiran sodium, and inotersen sodium were prohibited for 14 days or 5 half-lives, whichever is longer, before the first dose of the study drug and throughout the study period.

A total of 49 randomized subjects (17 in the placebo group, 16 in the acoramidis 400 mg group, 16 in the acoramidis 800 mg group) received the study drug and all were included in the safety analysis set. Patients with ATTRv-CM enrolled accounted for 28.6% (14 of 49) of the overall study population. None discontinued the study.

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35) Patients with ATTRv-CM were enrolled to account for approximately 30% of the study population.
36) Patients with monoclonal gammopathy of undetermined significance require a definitive diagnosis of ATTR-CM performed by amyloid typing with biopsy specimen (MS)
37) Dose adjustment with ≤50% and no categorical changes of drugs
38) ALT or AST >3 times the ULN or total bilirubin >2 times the ULN

Table 40 shows incidences of all adverse events and events reported by ≥2 subjects in any group.

Table 40. Incidences of adverse events (safety analysis set)

MedDRA PT	Placebo (n = 17)	Acoramidis	
		400 mg (n = 16)	800 mg (n = 16)
All adverse events	88.2 (15)	62.5 (10)	68.8 (11)
Constipation	11.8 (2)	6.3 (1)	18.8 (3)
Diarrhoea	0 (0)	12.5 (2)	18.8 (3)
Atrial fibrillation	5.9 (1)	6.3 (1)	12.5 (2)
Pain in extremity	5.9 (1)	0 (0)	12.5 (2)
Dizziness	0 (0)	0 (0)	12.5 (2)
Muscle spasms	11.8 (2)	6.3 (1)	6.3 (1)
Fluid retention	11.8 (2)	0 (0)	6.3 (1)
Fatigue	11.8 (2)	0 (0)	6.3 (1)
Headache	11.8 (2)	0 (0)	6.3 (1)
Venous pressure jugular increased	0 (0)	12.5 (2)	0 (0)
Oedema peripheral	0 (0)	12.5 (2)	0 (0)
Dyspnoea	11.8 (2)	6.3 (1)	0 (0)
Palpitations	17.6 (3)	0 (0)	0 (0)
Contusion	11.8 (2)	0 (0)	0 (0)
Fall	11.8 (2)	0 (0)	0 (0)
Cough	11.8 (2)	0 (0)	0 (0)
Pollakiuria	11.8 (2)	0 (0)	0 (0)

Incidence (%) (number of subjects with events)

No adverse events leading to death or adverse events leading to discontinuation of the study drug occurred.

Serious adverse events occurred in 11.8% (2 of 17) of subjects in the placebo group (atrial fibrillation and cardiac failure congestive; and cellulitis in 1 subject each) and 6.3% (1 of 16) of subjects in the acoramidis 400 mg group (dyspnoea), and a causal relationship to the study drug was ruled out for all of them.

7.3 Phase III studies

7.3.1 Foreign phase III study (Study AG10-301, CTD 5.3.5.1-2, study period, April 2019 to May 2023)

A placebo-controlled, randomized, double-blind study was conducted at 95 study centers outside Japan to evaluate the efficacy for superiority of acoramidis to placebo in non-Japanese patients with ATTRwt-

CM or ATTRv-CM (target sample size, 510 subjects[39] [170 in the placebo group and 340 in the acoramidis group]).

This study consisted of a screening period up to 35 days, a double-blind treatment period of 30 months to be covered by the primary analysis, and a follow-up period of 30 days. Of the double-blind treatment period, a part of the first 12 months was specified as Part A, and the whole was specified as Part B.

In this study, patients with ATTR-CM[40] aged ≥18 and ≤90 years, who had NYHA Class I to III symptoms and met the criteria below were mainly included.

- Patients who received a definitive diagnosis of ATTRwt-CM or ATTRv-CM confirmed by either of the following examinations and genotyping:
  (a) TTR amyloid deposition documented by amyloid typing (immunohistochemical staining, MS, or immunoelectron microscopy) with endomyocardial biopsy specimen; or
  (b) Positive image documented by ^{99m}Tc pyrophosphate or ^{99m}Tc bisphosphonate scintigraphy (3,3-diphosphono-1,2-propanodicarboxylic acid [DPD] or hydroxymethylene diphosphonate [HMDP/HDP]) and amyloid light-chain (AL) amyloidosis ruled out by serum and urine immunofixation as well as serum free immunoglobulin light chain test[41]
- Patients who have a history of cardiac failure meeting either of the following criteria:
  (a) Have a history of hospitalization due to cardiac failure; or
  (b) Have no history of hospitalization due to cardiac failure but have clinical evidence of cardiac failure manifested by signs or symptoms of volume overload or elevated intracardiac pressures (elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral oedema, etc.); or
  (c) Have heart failure symptoms that required or require ongoing treatment with a diuretic
- For patients taking cardiovascular medical therapy except for diuretics, those who had been on stable doses for at least 2 weeks before screening[37]
- Patients who have completed ≥150 m on the 6-minute walk test on at least 2 consecutive tests >24 hours to ≤3 weeks apart before randomization with a difference in distance walked ≤15%[42]

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39) The target sample size was established based on the hypothesis, described below, for the primary endpoint in Part B as specified at the start of this study, "Hierarchical composite endpoint of all-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30." With reference to Study ATTR-ACT, a clinical study of tafamidis, (*N Engl J Med.* 2018;379:1007-16), the following assumption was applied: all-cause mortality at Month 30 was 40% in the placebo group; the hazard ratio of acoramidis to placebo was 0.7; and frequency of cardiovascular-related hospitalization at up to Month 30 was 0.46 times per year in the placebo group and 0.3 times per year in the acoramidis group. The number of subjects needed to detect a significant difference between the groups according to Finkelstein-Schoenfeld method at a significance level of 4% (two-sided) with a power of 90% in a study where subjects were randomized to the placebo or acoramidis group in a 1:2 ratio was calculated to be 460. On the assumption that approximately 10% of subjects enrolled were found to have eGFR at baseline <30 mL/min/1.73 m^2 and thus excluded from the modified intent-to-treat (mITT) population, the primary efficacy analysis set, the target sample size of 510 was established.
After the start of the study, the time to allow start of concomitant use of tafamidis [see Footnote 44] and the primary endpoint in Part B were changed [see Footnote 50]. According to these changes, [redacted]. Because results from simulations based on multiple assumptions indicated that the power of >80% in the Finkelstein-Schoenfeld method could be maintained, the target sample size was kept unchanged.

40) Patients with ATTRv-CM were enrolled to account for approximately 20% of the study population.

41) Patients with monoclonal gammopathy of undetermined significance require a definitive diagnosis of ATTR-CM performed by amyloid typing with biopsy specimens (MS, immunoelectron microscopy, or immunohistochemistry)

42) If one of the first 2 tests does not achieve ≥150 m of distance walked or a difference in distance walked between the first 2 tests is not within 15%, the third test should be performed within 3 weeks from the first test. If the third test does not achieve ≥150 m of distance walked or a difference in distance walked between either of the first 2 tests and the third test is not within 15%, the concerned subject is not eligible for participation.

- Patients with NT-proBNP ≥300 pg/mL at screening
- Patients with left ventricular wall (interventricular septum or left ventricular posterior wall) thickness ≥12 mm as measured by transthoracic echocardiogram or cardiac magnetic resonance imaging (MRI) within 10 years before screening

The main exclusion criteria are as follows:
- Patients who are found to have abnormal liver function test values[43] at screening
- Patients who have eGFR <15 mL/min/1.73 m^2 at screening

Patients enrolled in this study were randomized to the placebo or acoramidis group in a 1:2 ratio using the disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), and eGFR at screening (≥45 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2) as stratification factors.

In this study, placebo or acoramidis 800 mg was administered orally twice daily.

Tafamidis was prohibited from 14 days before the first dose of the study drug to Month 12.[44] The following drugs were prohibited for various periods before the first dose of the study drug and then throughout the study period: Diflunisal, doxycycline hydrochloride hydrate, green tea extract, tauroursodeoxycholic acid, and ursodeoxycholic acid prohibited for 14 days; patisiran sodium for 90 days; inotersen sodium for 180 days; and other gene silencing drugs for their 5 half-lives.

A total of 632 randomized subjects (211 in the placebo group and 421 in the acoramidis group) received the study drug and all were included in the safety analysis set. All of 632 subjects (211 and 421) with the post-baseline efficacy evaluation data from at least 1 timepoint were included in the intent-to-treat (ITT) population, and of them, 611 subjects with eGFR at baseline ≥30 mL/min/1.73 m^2 (202 [182 with wild-type and 20 with variant][45] and 409 [370 with wild-type and 39 with variant][46]) were included in the modified intent-to-treat (mITT) population, which was used as the primary efficacy analysis set. Patients with ATTRv-CM enrolled accounted for 9.7% (61 of 632) of the overall study population. In the safety analysis set, 194 subjects (70 and 124) discontinued the study mainly because of death in 61 subjects (22 and 39), adverse events/cardiovascular-related hospitalization/events of clinical interest in 58 subjects (18 and 40), patients' decision in 31 subjects (13 and 18), consent withdrawal in 12 subjects (3 and 9), and need for treatment not permitted in this study in 9 subjects (1 and 8). In the mITT population, 22.8% (46 of 202) of subjects in the placebo group and 14.9% (61 of 409) of subjects in the acoramidis group started concomitant use of tafamidis at Month 12 or later.[47]

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43) ALT or AST >3 times the ULN or total bilirubin >3 times the ULN

44) As tafamidis was approved in some of participating countries after the start of this study, the time to permit concomitant use of tafamidis was changed from Month 24 to Month 12 (Protocol version 3.0 dated [redacted], 20[redacted]).

45) Disposition on disease type based on data entered via an automated voice-guided/interactive web response system by the investigators at randomization is shown. For disease type based on eCRF, 182 subjects had wild-type TTR, 19 subjects had variant TTR, and 1 subject had unknown type of TTR. For genotype, of patients with ATTRv-CM, 12 subjects had V122I, 2 had T60A, 1 subject had E89Q, and 4 subjects had the other mutations.

46) Disposition on disease type based on data entered via an automated voice-guided/interactive web response system by the investigators at randomization is shown. For disease type based on eCRF, 371 subjects had wild-type TTR, 37 subjects had variant TTR, and 1 subject had unknown type of TTR. For genotype, of patients with ATTRv-CM, 23 subjects had V122I, 3 subjects had T60A, and 11 subjects had the other mutations.

47) A total of 9 subjects started receiving tafamidis before Month 12, deviating from the protocol, but they were included in the efficacy analysis (mITT population).

Part A primary efficacy endpoint was change in 6-minute walk test distance from baseline to Month 12. Part B primary efficacy endpoint was a hierarchical composite endpoint[48)] consisting of all-cause mortality,[49)] frequency of cardiovascular-related hospitalization,[50)] change in NT-proBNP from baseline, and change in 6-minute walk test distance from baseline to Month 30. To control type I error in the study overall, significance levels of 1% (two-sided) and 4% (two-sided) were assigned to Parts A and B, respectively, for analyses on the primary endpoint. The applicant planned to submit the application based on the results from Part A in the event that all the subjects completed Part A, and comparison of results of the primary endpoint in Part A between the groups demonstrated superiority of acoramidis to placebo.

Table 41 shows results of the primary endpoint in Part A, and no significant difference was noted between the acoramidis and placebo groups.

Table 41. Change in 6-minute walk test distance (m) from baseline to Month 12 (mITT)

	Placebo (n = 201)	Acoramidis (n = 406)
Baseline	352.394 ± 93.0245 (201)	363.609 ± 103.1888 (404)
Month 12	353.474 ± 113.5159 (160)	359.601 ± 118.6608 (322)
Change from baseline to Month 12 Least squares mean [99% CI][a]	-24.54 [-41.25, -7.83]	-26.51 [-40.38, -12.65]
Difference from placebo Least squares mean [99% CI][a] *P* value[b]	-	-1.97 [-18.24, 14.30] *P* = 0.7550

Mean ± SD (number of subjects)

a Mixed models repeated measures (MMRM) (on an unstructured variance-covariance matrix) using disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2), dose group, timing of evaluation, and interaction between dose group and time of evaluation as fixed effects and baseline value as a covariate. Missing data after the first dose of the study drug were handled as follows: For missing data due to discontinuation, the jump to reference multiple imputation approach was applied, and for missing data due to death, the imputation was performed by replacement with the bottom 5% value of measured data in the same group at the same timing of evaluation as those in which the death occurred.

b Significance level of 1% (two-sided)

Results for the hierarchical composite endpoint, the primary endpoint in Part B, demonstrated superiority of acoramidis to placebo ($P < 0.0001$, significance level of 4% [two-sided], Finkelstein-

48) The primary endpoint in the original version of the protocol (Protocol version 1.0 dated [redacted], 20[redacted]) was "Hierarchical composite endpoint of all-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30." In Protocol version 5.0 (dated March 31, 2021), change in 6-minute walk test distance from baseline was added to the primary endpoint. Then, after the disclosure of results from comparisons of 6-minute walk test distance and NT-proBNP between the groups (December 27, 2021), change in NT-proBNP from baseline was added to the primary endpoint as a component superior to change in 6-minute walk test distance from baseline (Protocol version 6.0 dated June 16, 2022).

49) All-cause mortality events included death from any cause, heart transplant, and use of a cardiac mechanical assist device.

50) Cardiovascular-related hospitalization events included cardiovascular-related hospitalization (non-elective hospitalization for acute care of a cardiovascular-related pathological condition, requiring a stay for ≥24 hours [or over a period of more than 1 date if the time of admission/discharge is unknown]) and events of clinical interest (unscheduled visit for <24 hours to administer diuretics intravenously for decompensated cardiac failure).

Schoenfeld method[51]). Whether death or hospitalization of a subject was cardiovascular-related was determined at the independent clinical events committee in a blinded manner.

Table 42 shows the results of each primary endpoint component.

Table 42. Results of each primary endpoint component up to Month 30 (mITT)

	Placebo (n = 202)	Acoramidis (n = 409)
All-cause mortality (incidence % [number of subjects with the event])	25.7 (52)	19.3 (79)
Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) Mean ± SD (number of subjects with events/number of subjects analyzed)	0.293 ± 0.5751 (50/150)	0.132 ± 0.3257 (68/330)
NT-proBNP (pg/mL)		
Baseline	2650.11 ± 1899.482 (202)	2865.33 ± 2149.639 (409)
Measured value at Month 30	4348.33 ± 4758.130 (133)	2853.70 ± 2876.953 (280)
Ratio to baseline Adjusted geometric mean [95% CI][a]	2.771 [2.485, 3.091]	1.465 [1.356, 1.583]
6-minute walk test distance (m)		
Baseline	351.51 ± 93.828 (202)	362.78 ± 103.501 (407)
Measured value at Month 30	322.38 ± 120.916 (121)	365.96 ± 124.734 (269)
Change from baseline Least squares mean [95% CI][a]	-104.29 [-119.53, -89.06]	-64.65 [-75.45, -53.86]

Mean ± SD (number of subjects)

a MMRM (on an unstructured variance-covariance matrix; an analysis on proBNP was performed in a model with NT-proBNP at screening [≤3000 pg/mL or >3000 pg/mL] excluded) using disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2), dose group, timing of evaluation, and interaction between dose group and time of evaluation as fixed effects and baseline value as a covariate. Missing data after the first dose of the study drug were handled as follows: For missing data due to discontinuation, the jump to reference multiple imputation approach was applied, and for missing data due to death, the imputation was performed by replacement with the bottom 5% value of measured data in the same group at the same timing of evaluation as those in which the death occurred.

Table 43 shows detailed data on all-cause mortality and cardiovascular-related hospitalization. Figure 2 shows the Kaplan-Meier curve for time to all-cause mortality.

[51] According to the Finkelstein-Schoenfeld method (*Stat Med.* 1999;18:1341-54), hierarchical pairwise comparisons were performed between each subject and all the other subjects for "all-cause mortality," "frequency of cardiovascular-related hospitalization," "change in NT-proBNP from baseline," and "change in distance walked for 6 minutes from baseline," and the scores given in these comparisons were subjected to the test. The pairwise comparison for NT-proBNP gave a score (win [+1], tie [0], or loss [-1]) when the difference in change from baseline between subjects was ≥500 pg/mL; and the pairwise comparison for distance walked for 6 minutes gave a score (win [+1], tie [0], or loss [-1]) based on the presence or absence of the difference in change from baseline between subjects. These pairwise comparisons were initially planned to be performed in 8 strata using disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), and eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2) as stratification factors, but the stratum of a specific variant included ≤5 subjects. Based on the predetermined rule, subjects with any variant TTR were included in 1 stratum (a total of 5 strata). When the Finkelstein-Schoenfeld method was applied to data in this study, a zero score (tie [0]) (proceeded to next pairwise comparison for the less important component) was given to 71.9% of subjects for all-cause mortality, 44.9% for the frequency of cardiovascular-related hospitalization, 14.7% for change in NT-proBNP from baseline, and 0.4% for change in distance walked for 6 minutes.

Table 43. Detailed data on all-cause mortality and cardiovascular-related hospitalization (mITT)

	Placebo (n = 202)	Acoramidis (n = 409)
All-cause mortality	25.7 (52)	19.3 (79)
Death from any cause	24.8 (50)	19.3 (79)
Cardiovascular-related death	20.3 (41)	14.9 (61)
Non-cardiovascular-related death	4.5 (9)	4.4 (18)
Heart transplant	0.5 (1)	0 (0)
Use of cardiac mechanical assist device	0.5 (1)	0 (0)
Cardiovascular-related hospitalization	42.6 (86)	26.7 (109)
Cardiovascular-related hospitalization	39.1 (79)	24.7 (101)
Event of clinical interest	6.4 (13)	3.9 (16)

Incidence (%) (number of subjects with events)

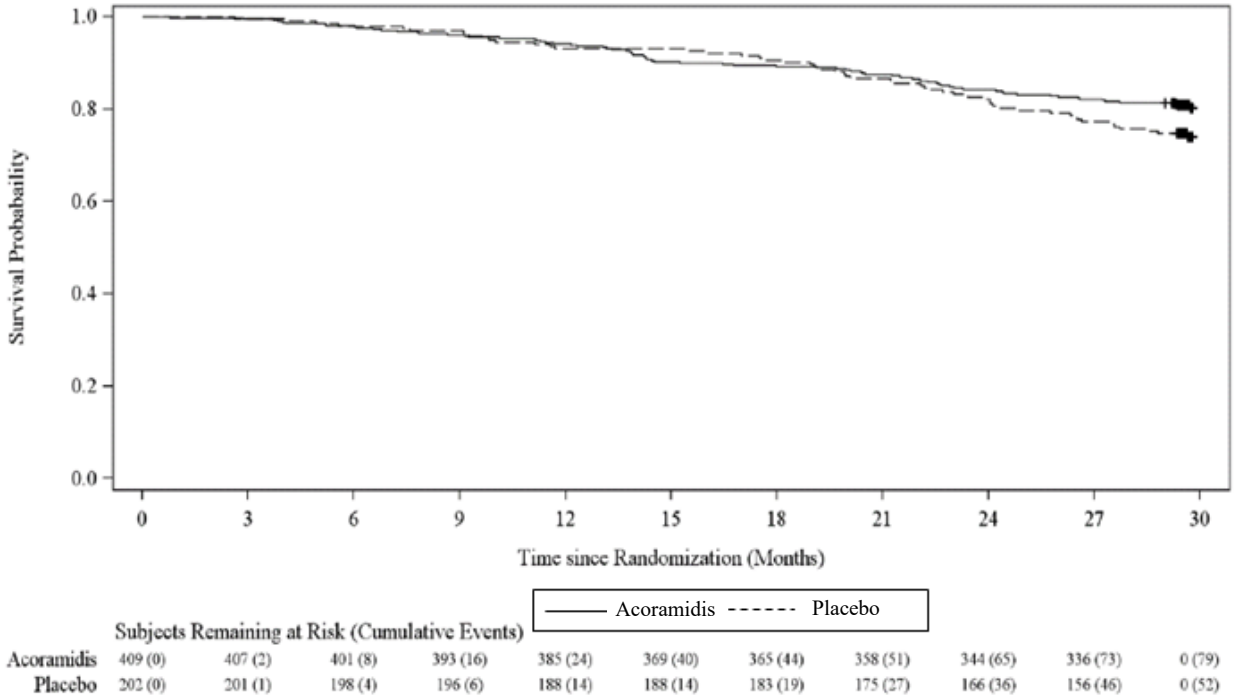

Figure 2. Time to all-cause mortality (Kaplan-Meier curve, mITT)

Table 42 shows results of changes in 6-minute walk test distance and NT-proBNP from baseline to Month 30, the secondary endpoints in Part B. Table 44 shows results of change in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score from baseline to Month 30.

Table 44. Change in KCCQ-OS score from baseline to Month 30 (mITT)

		Placebo (n = 202)	Acoramidis (n = 409)
KCCQ-OS score	Baseline	70.48 ± 20.651 (202)	71.73 ± 19.369 (408)
	Measured value at Month 30	64.15 ± 24.376 (136)	70.83 ± 22.165 (289)
	Change from baseline Least squares mean [95% CI][a]	-21.42 [-24.66, -18.18]	-11.48 [-13.79, -9.16]

Mean ± SD (number of subjects)

a MMRM (on an unstructured variance-covariance matrix) using disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2), dose group, timing of evaluation, and interaction between dose group and time of evaluation as fixed effects and baseline value as a covariate. Missing data after the first dose of the study drug were handled as follows: For missing data due to discontinuation, the jump to reference multiple imputation approach was applied, and for missing data due to death, the imputation was performed by replacement with the bottom 5% value of measured data in the same group at the same timing of evaluation as those in which the death occurred.

Table 45 shows the incidences of all adverse events and events reported by ≥10% of subjects in either group.

Table 45. Incidence of adverse events (safety analysis set)

MedDRA PT	Placebo (n = 211)	Acoramidis (n = 421)
All adverse events	97.6 (206)	98.1 (413)
Cardiac failure	39.3 (83)	24.0 (101)
COVID-19	14.2 (30)	21.1 (89)
Atrial fibrillation	21.8 (46)	16.6 (70)
Fall	18.5 (39)	15.9 (67)
Dyspnoea	19.0 (40)	12.4 (52)
Constipation	15.2 (32)	12.4 (52)
Urinary tract infection	13.3 (28)	12.1 (51)
Acute kidney injury	10.4 (22)	12.4 (52)
Diarrhoea	7.6 (16)	11.6 (49)
Arthralgia	10.9 (23)	11.4 (48)
Gout	8.1 (17)	11.2 (47)
Dizziness	10.9 (23)	10.9 (46)
Fatigue	12.3 (26)	10.0 (42)
Oedema peripheral	11.8 (25)	7.8 (33)

Incidence (%) (number of subjects with events)

Adverse events leading to death occurred in 17.1% (36 of 211) of subjects in the placebo group and 14.3% (60 of 421) of subjects in the acoramidis group. Adverse events reported by ≥1% of subjects in either group were cardiac failure (3.8% [8 subjects] in the placebo group and 4.3% [18 subjects] in the acoramidis group), cardiac failure chronic (0.9% [2 subjects] and 1.2% [5 subjects]), cardiac arrest (1.4% [3 subjects] and 0.5% [2 subjects]), and cardiorenal syndrome (1.4% [3 subjects] and 0% [0 subjects]). A causal relationship to the study drug was ruled out for all of the adverse events leading to death.

Serious adverse events occurred in 64.9% (137 of 211) of subjects in the placebo group and 54.6% (230 of 421) of subjects in the acoramidis group. Adverse events reported by ≥5% of subjects in either group were cardiac failure (18.5% [39 subjects] in the placebo group and 10.7% [45 subjects] in the acoramidis group), cardiac failure acute (6.6% [14 subjects] and 5.0% [21 subjects]), acute kidney injury (3.8% [8 subjects] and 5.0% [21 subjects]), and atrial fibrillation (7.1% [15 subjects] and 4.5% [19 subjects]). A causal relationship to the study drug could not be ruled out for the serious adverse events of cardiac failure acute and syncope/hypotension in 1 subject each in the acoramidis group.

Adverse events leading to discontinuation of the study drug occurred in 8.5% (18 of 211) of subjects in the placebo group and 9.3% (39 of 421) of subjects in the acoramidis group. Adverse events reported by ≥1% of subjects in either group were cardiac failure (0.9% [2 subjects] in the placebo group and 1.2% [5 subjects] in the acoramidis group). A causal relationship to the study drug could not be ruled out for the adverse events leading to discontinuation of the study drug of electrocardiogram QT prolonged in 1 subject in the placebo group and rash erythematous, abdominal discomfort, abdominal pain upper, nausea, dizziness/tremor, dyspepsia, dyspepsia/decreased appetite, and decreased appetite in 1 subject each in the acoramidis group.

7.3.2 Japanese phase III study (Study ALXN2060-TAC-302, CTD 5.3.5.2-1, ongoing since November 2020, data cut off on [redacted], 20[redacted])

An open-label, uncontrolled study was conducted at 12 study centers in Japan to evaluate efficacy, safety, PK, and PD of acoramidis in Japanese patients with ATTRwt-CM or ATTRv-CM (target sample size, 22 subjects[52)]).

This study consisted of a screening period up to 35 days, an open-label treatment period of 30 months to be covered by the primary analysis, an extension treatment period until approval of acoramidis in Japan or Month 30, whichever comes earlier,[53)] and a follow-up period of 30 days. Of the open-label treatment period, a part of the first 12 months was specified as Part A, and the whole was specified as Part B. When the study was planned, an analysis on the endpoints in Part A was planned to be performed at the time of completion of Part A. However, Part A in Study AG10-301 did not demonstrate superiority of acoramidis to placebo for the primary endpoint, and thus the plan was changed to perform all the analyses on the endpoints including those in Part A at the time of completion of Part B.

The main inclusion and exclusion criteria are the same as those in Study AG10-301 except for the details shown in Table 46.

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52) The target sample size was established based on the feasibility. For "All-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30," the primary endpoint in Part B, a probability of meeting both of the criteria described below was calculated to be ≥80% on the assumption that the sample sizes in Study AG10-301 was 460 and Study ALXN2060-TAC-302 was 19, using the estimates in sample size establishment for Study AG10-301.
- For all-cause mortality at Month 30, a hazard ratio in Study AG10-301 and a point estimate of a hazard ratio of results in Study ALXN2060-TAC-302 compared with those in the placebo group in Study 301 are below 1.
- For the frequency of cardiovascular-related hospitalization at Month 30, a risk ratio in Study AG10-301 and a point estimate of a risk ratio of results in Study ALXN2060-TAC-302 compared with those in the placebo group in Study AG10-301 are below 1.

With a dropout rate of approximately 10% to 15% at Month 12 taken into account, the target sample size of 22 was established.

53) In Protocol version 5.0 (dated September 11, 2023), the extension treatment period was extended from 24 to 30 months.

Table 46. Differences in the main inclusion and exclusion criteria between Studies AG10-301 and ALXN2060-TAC-302

	Study AG10-301	Study ALXN2060-TAC-302
Inclusion criteria		
Age range	≥18 and ≤90 years	≥20 and ≤90 years
Examination method for definitive diagnosis of ATTR-CM	(b) Positive image documented by ^{99m}Tc pyrophosphate or ^{99m}Tc bisphosphonate scintigraphy (DPD or HMDP/HDP) and AL amyloidosis ruled out by serum and urine immunofixation as well as serum free immunoglobulin light chain test	(b) Positive image documented by ^{99m}Tc pyrophosphate or ^{99m}Tc bisphosphonate scintigraphy (DPD or HMDP/HDP), AL amyloidosis ruled out by serum and urine immunofixation as well as serum free immunoglobulin light chain test, and TTR amyloid deposition documented with non-cardiac biopsy specimen (abdominal wall fat, etc.)
Exclusion criteria		
eGFR at screening	eGFR at screening <15 mL/min/1.73 m^2	eGFR at screening <30 mL/min/1.73 m^2

In this study, acoramidis 800 mg was administered orally twice daily.

The same rules for prohibited concomitant drugs as those in Study AG10-301 were applied except for tafamidis, which was prohibited from 14 days before the first dose of the study drug and throughout the study period.

A total of the 25 subjects enrolled (23 with wild-type TTR and 2 with variant TTR[54]) received the study drug and all were included in the safety analysis set and full analysis set (FAS). The FAS was used as the primary efficacy analysis set. A total of 3 subjects discontinued the study because of consent withdrawal in 2 subjects and adverse events in 1 subject.

Table 47 shows results of change in 6-minute walk test distance from baseline to Month 12, the primary endpoint in Part A. The lower limit of 95% CI of the least squares mean exceeded −60 m,[55] the criterion for success in Part A.

Table 47. Change in 6-minute walk test distance (m) from baseline to Month 12 (FAS)

	Overall (n = 25)
Baseline	399.74 ± 70.434 (25)
Month 12	403.66 ± 68.741 (23)
Change from baseline to Month 12 Least squares mean [95% CI][a]	-3.86 [-22.85, 15.13]

Mean ± SD (number of subjects)

a MMRM (on an unstructured variance-covariance matrix, data up to Month 30 included in the analysis) using the baseline value and timing of evaluation as fixed effects. Missing data due to death, heart transplant, or use of a cardiac mechanical assist device were imputed by replacement with the bottom 25% of measured data at the same timing of evaluation as that with missing measurement, and the other missing data were not imputed.

Table 48 shows results of all-cause mortality[48] and frequency of cardiovascular-related hospitalization at up to Month 30,[49] the primary endpoint in Part B. The survival at Month 30 (100%) exceeded that (74.3%) in the placebo group in Study AG10-301, the criterion for success in Part B. Whether death or

54) For genotype, of patients with ATTRv-CM, 1 had V30M, and the other had D38A.

55) Based on the mean change in distance walked for 6 minutes from baseline to Month 12 in the placebo group in Study ATTR-ACT of tafamidis (*N Engl J Med.* 2018;379:1007-16), which was -60 m, the threshold of "-60 m" was specified.

hospitalization of a subject was cardiovascular-related was determined at the independent clinical events committee in a blinded manner.

Table 48. All-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30 (FAS)

	Overall (n = 25)
All-cause mortality (incidence % [number of subjects with the event])	0 (0)
Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) [95% CI][a] (number of subjects with events/number of subjects analyzed)	0.1329 [0.0511, 0.3457] (5/25)

a Negative binomial regression model not including the covariate with the offset term of logarithmic study duration for each subject

Table 49 shows detailed data on cardiovascular-related hospitalization.

Table 49. Detailed data on cardiovascular-related hospitalization (FAS)

	Overall (n = 25)
Cardiovascular-related hospitalization	20.0 (5)
Cardiovascular-related hospitalization	20.0 (5)
Event of clinical interest	0 (0)

Incidence (%) (number of subjects with events)

Table 50 shows results of changes in 6-minute walk test distance, KCCQ-OS score, and NT-proBNP from baseline to Month 30, the secondary endpoints and exploratory endpoint in Part B.

Table 50. Changes in 6-minute walk test distance, KCCQ-OS score, and NT-proBNP from baseline to Month 30 (FAS)

	6-minute walk test distance (m)	KCCQ-OS score	NT-proBNP (pg/mL)
Baseline	399.74 ± 70.434 (25)	75.63 ± 21.735 (25)	2562.0 ± 1781.21 (25)
Measured value at Month 30	372.95 ± 79.935 (22)	70.15 ± 20.784 (22)	2434.5 ± 1798.07 (22)
Change from baseline Least squares mean [95% CI][a]	-36.20 [-58.54, -13.86]	-6.97 [-14.74, -0.80]	1.06 [0.88, 1.26][b]

Mean ± SD (number of subjects)

a MMRM (on an unstructured variance-covariance matrix) using the baseline value and timing of evaluation as fixed effects. Missing data due to death, heart transplant, or use of a cardiac mechanical assist device were imputed by replacement with the bottom 25% of measured data at the same timing of evaluation as that with missing measurement, and the other missing data were not imputed.

b Ratio to baseline (adjusted geometric mean [95% CI])

Table 51 shows the incidence of all adverse events and events reported by ≥10% of subjects overall.

Table 51. Incidence of adverse events (safety analysis set)

MedDRA PT	Overall (n = 25)
All adverse events	100 (25)
Constipation	28.0 (7)
Pyrexia	20.0 (5)
Nasopharyngitis	24.0 (6)
Back pain	20.0 (5)
COVID-19	16.0 (4)
Haematuria	16.0 (4)
Renal dysfunction	16.0 (4)
Cardiac failure	12.0 (3)
Vomiting	12.0 (3)
Arthralgia	12.0 (3)
Rash	12.0 (3)

Incidence (%) (number of subjects with events)

No adverse events leading to death occurred.

Serious adverse events occurred in 48.0% (12 of 25) of subjects, and adverse events reported by ≥2 subjects were large intestine polyp in 8.0% (2 of 25) of subjects. A causal relationship to the study drug was ruled out for all of the serious adverse events.

Adverse events leading to discontinuation of the study drug occurred in 8.0% (2 of 25) of subjects (renal dysfunction and drug eruption in 1 subject each), and a causal relationship to the study drug could not be ruled out for either of them.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about clinical positioning of acoramidis in treatment of ATTR-CM:

ATTR-CM is caused by deposition of TTR-derived amyloid fibrils in the cardiac muscle, and the TTR-derived amyloid fibrils are aggregates of misfolded TTR monomers released by dissociation of TTR tetramers in plasma destabilized. ATTR-CM can lead to restrictive cardiomyopathy, which would result in not only cardiac failure symptoms and arrhythmia due to conductive abnormality but also fatal consequences. The 2020 Guideline on Diagnosis and Treatment of Cardiac Amyloidosis indicates liver transplant and drug therapy for treatment of ATTR-CM, but the liver transplant outcomes vary depending on genotype and age and are indicated for an extremely limited fraction of the patients, while drug therapy should be considered first. For the drug therapy, a drug approved for treatment of ATTR-CM in Japan is only tafamidis, which can act as a TTR stabilizer. Acoramidis has the same mechanism of action as that of tafamidis but is demonstrated to have higher binding affinity to TTR than tafamidis (*J Med Chem.* 2018;61:7862-76, *Proc Natl Acad Sci U S A.* 2013;110:9992-7, etc.). The foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) in patients with documented ATTRwt-CM or ATTRv-CM accompanied by cardiac failure have demonstrated that acoramidis has efficacy and acceptable safety. Acoramidis can be used in patients with ATTRwt-CM or ATTRv-CM and thus will be positioned as with tafamidis in clinical settings. Concomitant use of tafamidis was allowed at Month 12 and afterward[44)] in Study AG10-301 to prevent dropout of patients in this placebo-controlled study, but concomitant use of acoramidis with tafamidis is not presumed in clinical settings.

PMDA's view:
Studies AG10-301 and ALXN2060-TAC-302 demonstrated the efficacy and safety of acoramidis in patients with ATTRwt-CM or ATTRv-CM accompanied by cardiac failure [see Section "7.R.3 Efficacy" and "7.R.4 Safety"]. Thus, in the clinical setting, acoramidis will be positioned similarly to tafamidis for this patient population. Liver transplant is one of treatment options for ATTR-CM but indicated for limited patients, and tafamidis is the only a drug approved for treatment of ATTR-CM in Japan. In this view, it is meaningful to make acoramidis available in the clinical setting as an additional accessible treatment option.

7.R.2 Feasibility of using foreign clinical study data

The applicant's explanation about development strategy of acoramidis in Japan:
The development of acoramidis for patients with ATTR-CM first began abroad. Due to the difficulty in participating to the foreign phase III study (Study AG10-301) at the time of development planning in Japan, the applicant conducted a Japanese phase III study (Study ALXN2060-TAC-302) separately. After confirmation of the similarities in the efficacy and safety of acoramidis in Japanese patients to those in non-Japanese patients, the efficacy and safety of acoramidis in Japanese patients with ATTR-CM were evaluated utilizing data from Study AG10-301. For the comparison of results between the studies, Study ALXN2060-TAC-302 should have been designed with a control group as with Study AG10-301. However, in Japan, tafamidis was already available for ATTR-CM at the time of study planning, and this precluded a long-term placebo-controlled study in patients with ATTR-CM, a progressive and serious disease with a poor prognosis, from a viewpoint of difficulty in obtaining consent from patients. Accordingly, Study ALXN2060-TAC-302 was conducted as an open-label, uncontrolled study.

The validity of the use of results from Study AG10-301 to explain the efficacy of acoramidis in Japanese patients with ATTR-CM was examined as described below, based on intrinsic and extrinsic ethnic factors potentially affecting the efficacy evaluation of acoramidis and comparison of patient characteristics between Studies AG10-301 and ALXN2060-TAC-302.

For intrinsic ethnic factors, no clear differences in pathological condition or mechanism of development of ATTR-CM between Japanese and non-Japanese patients were reported, and no clear differences were observed in PK or PD between Japanese and non-Japanese patients after administration of acoramidis [see Section "6.R.1 Differences in PK and PD of acoramidis between Japanese and non-Japanese subjects"]. For extrinsic ethnic factors, a diagnosis of ATTR-CM is made based on clinical symptoms and examination findings, electrocardiogram findings, findings obtained by multiple imaging technologies, findings from biopsy specimens, and/or genotyping results in combination, and currently non-invasive bone scintigraphy can be also used for the diagnosis in combination with other technologies. Similar diagnostic criteria have been applied in and outside Japan. For ATTR-CM, tafamidis is the only approved product as disease-modifying drug in and outside Japan, and there are no marked differences between Japan and other countries in the treatment strategies providing supportive therapies for cardiovascular complications.

Table 52 compares patient characteristics between the studies. Patients in Study ALXN2060-TAC-302 had shorter time from the initial diagnosis of ATTR-CM and were more likely to have NYHA Class II symptoms and have previously received tafamidis than those in Study AG10-301, and no patients started tafamidis after the start of the study. The other patient characteristics did not remarkably differ between the studies.

Table 52. Comparison of patient characteristics between Studies AG10-301 (mITT) and ALXN2060-TAC-302 (FAS)

		Study AG10-301		Study ALXN2060-TAC-302 (n = 25)
		Placebo (n = 202)	Acoramidis (n = 409)	
Age (year)[a]		76.96	77.32	76.5
BMI (kg/m^2)[a]		26.97	27.07	23.35
Time from initial diagnosis of ATTR-CM (years)[b]		0.71 [0.0, 7.4]	0.83 [0.0, 10.1]	0.20 [0.0, 4.2]
NYHA Class	I	8.4 (17)	12.5 (51)	0 (0)
	II	77.2 (156)	70.4 (288)	96.0 (24)
	III	14.4 (29)	17.1 (70)	4.0 (1)
Proportion of patients previously treated with tafamidis		2.0 (4)	2.0 (8)	8.0 (2)
Proportion of patients who started tafamidis after start of the study		22.8 (46)	14.9 (61)	-

Proportion % (number of patients); -, Not applicable
a Mean
b Median [minimum, maximum]

Effects of the differences in patient characteristics between the above studies on all-cause mortality and frequency of cardiovascular-related hospitalization were investigated based on the results from the subgroup analysis in Study AG10-301 by patient characteristic (Table 53). Although interpretation of the results has limitations because of the presence of subgroups with a small sample size, no clear differences were observed in all-cause mortality or frequency of cardiovascular-related hospitalization between subgroups. The differences in patient characteristics between the studies are considered unlikely to affect the efficacy evaluation of acoramidis.

Based on the above findings, the applicant considers it possible to explain the efficacy of acoramidis in Japanese patients with ATTR-CM utilizing results from Study AG10-301.

Table 53. All-cause mortality and frequency of cardiovascular-related hospitalization in Study AG10-301 (mITT) by each of the patient characteristics that differed between Studies AG10-301 and ALXN2060-TAC-302

		Below the median[a]		At or above the median[a]	
		Placebo	Acoramidis	Placebo	Acoramidis
Time from initial diagnosis of ATTR-CM	All-cause mortality (incidence % [number of subjects with events])	20.0 (22)	15.8 (31)	32.6 (30)	22.6 (48)
	Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) (mean ± SD) (number of subjects with events/number of subjects analyzed)	0.26 ± 0.564 (26/86)	0.11 ± 0.314 (26/154)	0.34 ± 0.592 (24/64)	0.15 ± 0.336 (41/175)
		None		Yes	
		Placebo (n = 197)	Acoramidis (n = 401)	Placebo (n = 4)	Acoramidis (n = 8)
Prior use of tafamidis	All-cause mortality (incidence % [number of subjects with events])	25.4 (50)	19.2 (77)	25.0 (1)	25.0 (2)
	Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) (mean ± SD) (number of subjects with events/number of subjects analyzed)	0.29 ± 0.579 (47/147)	0.13 ± 0.328 (68/324)	- (3/3)	0 (0/6)
		None		Yes	
		Placebo (n = 156)	Acoramidis (n = 348)	Placebo (n = 46)	Acoramidis (n = 61)
First use of tafamidis after start of study	All-cause mortality (incidence % [number of subjects with events])	26.9 (42)	21.6 (75)	21.7 (10)	6.6 (4)
	Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) (mean ± SD) (number of subjects with events/number of subjects analyzed)	0.30 ± 0.613 (36/114)	0.14 ± 0.335 (57/273)	0.27 ± 0.439 (14/36)	0.11 ± 0.278 (11/57)

-, Not calculated

a For all-cause mortality, the median period in all the subjects was 0.79 years (below the median, 110 subjects in the placebo group and 196 subjects in the acoramidis group; and at or above the median, 92 subjects in the placebo group and 212 subjects in the acoramidis group). For the frequency of cardiovascular-related hospitalization, the median period in all the surviving subjects was 0.73 years (below the median, 107 subjects in the placebo group and 184 subjects in the acoramidis group; at or above the median, 95 subjects in the placebo group and 224 subjects in the acoramidis group).

PMDA's view:

For the efficacy evaluation, data on all-cause mortality and frequency of cardiovascular-related hospitalization, components of the primary endpoint in Study ALXN2060-TAC-302, should have been compared with the corresponding data from the control group with subjects randomized within the same study, as these components are likely to be affected by patient characteristics of the study population. However, it was inevitable for the applicant to conduct Study ALXN2060-TAC-302 as open-label uncontrolled study, in view of the applicant's explanation about feasibility of the placebo-controlled study and the limited number of patients with ATTR-CM in Japan that was unlikely to lead to sufficient number of events for between-group comparison within the study.

In view of the following points, PMDA considers it acceptable to explain the efficacy of acoramidis in Japanese patients with ATTR-CM utilizing results from Study AG10-301:

- No clear differences are observed in intrinsic or extrinsic ethnic factors potentially affecting the efficacy evaluation of acoramidis between Japan and countries outside Japan.
- Although differences were observed in some patient characteristics between the populations enrolled in Studies AG10-301 and ALXN2060-TAC-302, the efficacy of acoramidis did not clearly differ between any pairs of the subgroups formed according to the concerned patient characteristics in Study AG10-301.

7.R.3 Efficacy

7.R.3.1 Appropriateness of primary endpoint

The applicant's explanation about appropriateness of the primary endpoint and analysis plan in the foreign phase III study (Study AG10-301):

In Study AG10-301, the primary endpoint in Part A was change in 6-minute walk test distance from baseline to Month 12; and the primary endpoint in Part B was a hierarchical composite endpoint consisting of all-cause mortality, frequency of cardiovascular-related hospitalization, change in NT-proBNP from baseline, and change in 6-minute walk test distance from baseline to Month 30. Although the true efficacy endpoint in treatment of ATTR-CM is improvement of survival outcome, ATTR-CM is a rare disease with a small patient population, which precludes conduct of a clinical study with sample size large enough to demonstrate the efficacy using only all-cause mortality as the primary endpoint. The Protocol version 1.0 (dated [redacted], 20[redacted]) of Study AG10-301 specified the primary endpoint as a hierarchical composite endpoint consisting of all-cause mortality and frequency of cardiovascular-related hospitalization, a clinically relevant event.

As tafamidis was approved in some participating countries after the start of Study AG10-301, the time to permit concomitant use of tafamidis during the study was changed from Month 24 to Month 12 (Protocol version 3.0 dated [redacted], 20[redacted]). Furthermore, the coronavirus disease 2019 (COVID-19) pandemic impeded patient enrollment, and patients using tafamidis concomitantly increased more than expected. These circumstances were predicted to lower the number of events, potentially leading to a decreased power in the primary analysis. However, the double-blind treatment period in Study AG10-301 was fixed as 30 months, and a part of the patients had already completed the study, making it difficult to change the target sample size and extend the study period. To ensure the power in the primary analysis, a total of 2 changes, before unblinding in Part A and after disclosure of the results from Part A, were made to the primary endpoint as described below. The second change after disclosure of the results from Part A was made based on the results of blinded data review.[56)]

- The 6minute walk test distance is an indicator of exercise tolerance in patients with cardiac failure. Thus, change in the 6-minute walk test distance from baseline was added as the least-prioritized component in the hierarchical composite endpoint, the primary endpoint (Protocol version 5.0, dated March 31, 2021).
- NT-proBNP is a biomarker of which measurement is recommended for clinical management of cardiac failure and cardiomyopathy. Change in NT-proBNP from baseline was added as a component more important than the change in 6-minute walk test distance from baseline to the hierarchical composite endpoint, the primary endpoint (Protocol version 6.0, dated June 16, 2022).

The Finkelstein-Schoenfeld method applied to the primary analysis enables inter-group comparisons of multiple components in a hierarchical manner according to their clinical importance and thus allowed all-cause mortality to be handled as the most important event among other events including frequency of cardiovascular-related hospitalization. This method is considered appropriate for the efficacy

[56)] At the start of the study, the mortality and frequency of cardiovascular-related hospitalization in the placebo group were assumed to be 40% and 0.46 times per year, respectively, but the data review revealed that the mortality and frequency of cardiovascular-related hospitalization in the pooled population of the groups were 20% and 0.2 times per year, respectively, suggesting that these events would be far less likely to occur than initially assumed.

evaluation of acoramidis. The primary endpoints in Parts A and B of the Japanese phase III study (Study ALXN2060-TAC-302) were the same as the pre-change endpoints of Study AG10-301 and did not reflect the changes to the primary endpoints in Study AG10-301.

In Study AG10-301, the Part B primary endpoint changed twice after disclosure of the results of 6-minute walk test distance and NT-proBNP in the acoramidis and placebo groups in Part A (December 27, 2021). PMDA asked the applicant to explain the validity of the changes.

The applicant's explanation:
In this study, teams for conduct of Parts A and B were independently established, and information exchanges between the teams were restricted. The addition of change in NT-proBNP from baseline was made after disclosure of the study results from Part A, but it was based on the blinded data review where the results of NT-proBNP and 6-minute walk test distance in each group of Part A were not taken into account. During the analyses of Part A endpoints, the frequency of cardiovascular-related hospitalization remained blinded, and the composite endpoint consisting of all-cause mortality and frequency of cardiovascular-related hospitalization as well as each component were not subjected to open-label inter-group comparisons. Patient enrollment in Study AG10-301 was completed before the disclosure of Part A results, raising no concerns that characteristics of patients enrolled before and after the second change to the primary endpoint could have been different. Accordingly, this change is unlikely to give bias to the study results and thus not considered to compromise the study integrity.

PMDA's view:
The primary endpoint of Study AG10-301 changed several times when it was in progress. Especially, the addition of change from baseline in NT-proBNP to the hierarchical composite endpoint in the second change is not considered appropriate, because it was made in the situation where the sponsor and other parties concerned could have known the study results including over-time changes in NT-proBNP and changes in 6-minute walk test distance. The relationship between changes from baseline in 6-minute walk test distance and NT-proBNP after therapeutic intervention and improvement in survival outcome, the true efficacy endpoint in treatment of ATTR-CM, remains unclear at present. Both Part A primary endpoint and the revised Part B primary endpoint are considered inappropriate.

At the same time, the efficacy evaluation of acoramidis based on the results in Study AG10-301 is considered acceptable, in view of the following:

- Even at the start of Study AG10-301, all-cause mortality and frequency of cardiovascular-related hospitalization, potentially highly important parameters in clinical treatment of ATTR-CM, were included in the primary endpoint.
- Death and hospitalization were assessed at the independent clinical events committee in a blinded manner; whether these events met definitions of the efficacy endpoints in the protocol was objectively assessed.
- According to the applicant's explanation, at the time of completion of Part A analysis, information on the frequency of cardiovascular-related hospitalization remained blinded, and results of the composite endpoint consisting of all-cause mortality and frequency of cardiovascular-related hospitalization were not subjected to unblinded inter-group comparisons.

- After disclosure of the study results from Part A, no additional patients were enrolled; the disclosure of these study results would not cause bias in patient enrollment.

Based on the above points, the efficacy evaluation of acoramidis mainly focused on all-cause mortality and frequency of cardiovascular-related hospitalization among components of the hierarchical composite endpoint, the primary endpoint.

7.R.3.2 Evaluation results of efficacy

The applicant's explanation about evaluation results of efficacy in the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302):

Table 42 shows results for the hierarchical composite endpoint consisting of all-cause mortality, frequency of cardiovascular-related hospitalization, change in NT-proBNP from baseline, and change in 6-minute walk test distance from baseline up to Month 30, the primary endpoint in Part B of Study AG10-301, as well as those on each component, demonstrating superiority of acoramidis to placebo. In the analysis according to the Finkelstein-Schoenfeld method, pairwise comparisons were performed for 4 components of the hierarchical composite endpoint. Approximately 55% of the subjects were given scores (win [+1] or loss [−1]) in pairwise comparisons for clinically high-prioritized components, all-cause mortality and frequency of cardiovascular-related hospitalization. The survival analysis on all-cause mortality revealed that the hazard ratio [95% CI][57] of the acoramidis group to the placebo group was 0.772 [0.542, 1.102], which did not remarkably differ from the assumption (hazard ratio, 0.7) at the time of planning the study. Majority of all-cause mortality events were cardiovascular-related deaths (41 of 52 subjects in the placebo group and 61 of 79 subjects in the acoramidis group), and heart transplant and use of a cardiac mechanical assist device occurred in 1 subject each in the placebo group (Table 43). In Study AG10-301, the incidence of all-cause mortality and frequency of cardiovascular-related hospitalization both tended to be lower in the acoramidis group than in the placebo group irrespective of use of tafamidis after the start of the study (Table 53). As shown above, Study AG10-301 is considered to demonstrate the efficacy of acoramidis in treatment of ATTR-CM.

Table 48 shows results of all-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30, the primary endpoint in Part B of Study ALXN2060-TAC-302. The survival at Month 30 (100%) exceeded that (74.3%) in the placebo group in Study AG10-301, the criterion for success; the survival exceeded that in the placebo group as with the acoramidis group in Study AG10-301. Results of frequency of cardiovascular-related hospitalization and secondary endpoints in the patient population in Study ALXN2060-TAC-302 were generally similar to those in the acoramidis group in Study AG10-301 as well. A propensity score matching analysis was performed as a post hoc supplementary analysis. After patient characteristic factors potentially affecting prognosis of ATTR-CM were adjusted, results in Study ALXN2060-TAC-302 were compared with those in the placebo group in Study AG10-301 (Table 54). The incidence of all-cause mortality and frequency of cardiovascular-related hospitalization were both lower in the patient population in Study ALXN2060-TAC-302 than in the placebo group in Study AG10-301. On the assumption that the incidence of all-cause mortality in Study ALXN2060-

[57] Estimated in a stratified Cox proportional hazards model using the dose group and distance walked for 6 minutes at baseline as factors and disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), and eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2) as strata.

TAC-302 at up to Month 30 was 24.8% as that in the placebo group in Study AG10-301, a probability of no all-cause mortality events occurring in subjects of the sample size in Study ALXN2060-TAC-302 was estimated to be 0.08%.

Table 54. Results in propensity score matching analysis (mITT)

	Placebo group in Study AG10-301 (n = 50)	Study ALXN2060-TAC-302 (n = 25)
All-cause mortality (incidence % [number of subjects with the event])[a]	24.0 (12)	0 (0)
Frequency of cardiovascular-related hospitalization in surviving subjects (times per year)[a] (mean ± SD) (number of subjects with events/number of subjects analyzed)	0.61 ± 0.784 (21/39)	0.13 ± 0.299 (5/25)

a Propensity scores were calculated using age, sex, body mass index (BMI), NYHA Class (I/II or III), disease type (wild-type or variant), NT-proBNP, and 6-minute walk test distance as covariates at baseline. Results at the matching ratio of 1:2 are shown.

In view of investigation results for feasibility of using Study AG10-301 results and confirmed similarity of results of Study ALXN2060-TAC-302 to those of Study AG10-301, acoramidis is expected to have efficacy in Japanese patients with ATTR-CM as well.

PMDA's view:
In view of the following findings in Part B of Study AG10-301, the efficacy of acoramidis in patients with ATTR-CM has been demonstrated: Results of the primary endpoint demonstrated superiority of acoramidis to placebo. The results largely reflect the results of all-cause mortality and frequency of cardiovascular-related hospitalization, clinically high-prioritized components; the results of respective 2 components were lower in the acoramidis group than in the placebo group, with differences expected at the study planning. Study ALXN2060-TAC-302 with a small sample size of Japanese patients with ATTR-CM precluded precise comparison with Study AG10-301. However, the efficacy of acoramidis is likely to be promising in Japanese patients with ATTR-CM as well based on the results from these studies, in view of the following: The clinically high-prioritized components in Study ALXN2060-TAC-302 yielded similar results to those in the acoramidis group in Study AG10-301; and no marked differences were observed in intrinsic or extrinsic ethnic factors between Japanese and non-Japanese [see Section "7.R.2 Feasibility of using foreign clinical study data"]. The efficacy by severity based on NYHA Class of the symptoms is reviewed in Section "7.R.3.3 Efficacy by severity of cardiac failure," and the efficacy by disease type of ATTR-CM in Section "7.R.3.4 Efficacy by disease type of ATTR-CM."

7.R.3.3 Efficacy by severity of cardiac failure

The applicant's explanation about the effect of severity of cardiac failure (NYHA Class) on the efficacy of acoramidis:
Table 55 shows results of all-cause mortality and frequency of cardiovascular-related hospitalization, main components of the primary endpoint in the foreign phase III study (Study AG10-301), by NYHA Class at baseline. In the subgroup of NYHA Class I/II at baseline, the incidence of all-cause mortality and frequency of cardiovascular-related hospitalization were lower in the acoramidis group than in the placebo group. In the subgroup of NYHA Class III at baseline, however, the incidence of all-cause mortality was lower in the acoramidis group than in the placebo group, but the point estimate of the

hazard ratio exceeded 1. The mean frequency of cardiovascular-related hospitalization in surviving subjects was higher in the acoramidis group than in the placebo group. The statistical result on the incidence of all-cause mortality, of which the point estimate of the hazard ratio exceeded 1, is not necessarily considered to suggest that acoramidis would increase the incidence of mortality because the number of patients with NYHA Class III enrolled in Study AG10-301 is limited. The result on frequency of cardiovascular-related hospitalization in surviving subjects, which was higher in the acoramidis group than in the placebo group, might have been attributable to improved survival by acoramidis that would extend the observation period of the patients in a severe condition. Taking into account that the frequency of cardiovascular-related hospitalization in all the patients including those who died during the study was lower in the acoramidis group than in the placebo group, the concerned result is not considered to suggest that acoramidis would increase frequency of cardiovascular-related hospitalization.

In addition to the above, TTR stabilization rate[5)] did not clearly differ between the subgroups formed according to NYHA Class (Table 56). In view of these findings, the efficacy of acoramidis can be expected in patients with ATTR-CM who have NYHA Class III symptoms.

Table 55. All-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30 by NYHA Class in Study AG10-301 (mITT)

		Class I/II		Class III	
		Placebo (n = 173)	Acoramidis (n = 339)	Placebo (n = 29)	Acoramidis (n = 70)
All-cause mortality	% (number of subjects with events)	24.3 (42)	17.4 (59)	34.5 (10)	28.6 (20)
	Hazard ratio [95% CI][a]	0.695 [0.466, 1.036]		1.145 [0.515, 2.546]	
Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) (mean ± SD) (number of subjects with events/number of subjects analyzed)		0.31 ± 0.574 (47/131)	0.12 ± 0.297 (55/280)	0.18 ± 0.586 (3/19)	0.21 ± 0.449 (13/50)
Frequency of cardiovascular-related hospitalization in all the subjects (times per year) (mean ± SD) (number of subjects with events)		0.51 ± 0.856 (74)	0.25 ± 0.677 (87)	0.75 ± 1.107 (12)	0.47 ± 1.044 (22)

a Stratified Cox proportional hazards model using dose groups, baseline 6-minute walk test distance, baseline NYHA Class(I/II or III), and interaction between baseline NYHA Class and baseline 6-minute walk test distance as factors, and disease type (wild-type or variant), NT-proBNP at screening (≤3000 pg/mL or >3000 pg/mL), and eGFR at screening (<45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2) as strata.

Table 56. TTR stabilization rate (%) by NYHA Class in Study AG10-301 (mITT)

	Class I/II		Class III	
	Placebo	Acoramidis	Placebo	Acoramidis
Day 28 (pre-dose)	-2.20 [-85.74, 39.99] (41)	96.44 [12.51, 374.27] (93)	-2.33 [-38.20, 50.19] (8)	98.44 [4.34, 269.17] (17)
Month 12 (pre-dose)	3.32 [-363.82, 50.33] (34)	95.84 [-10.05, 166.85] (71)	10.72 [-53.09, 46.44] (5)	93.23 [60.88, 162.43] (12)
Month 30 (pre-dose)	9.19 [-455.67, 87.84] (27)	98.29 [29.72, 194.49] (70)	-19.98, 63.79[a] (2)	96.90 [95.26, 121.59] (11)

Median [minimum, maximum] (number of subjects)
a Individual values

PMDA's view:

Although investigation based on the results of the subgroup analysis has limitations, in view of the analysis results, the efficacy of acoramidis can be expected in the subgroup of patients with NYHA Class I/II. In the subgroup of patients with NYHA Class III, the mean frequency of cardiovascular-related hospitalization in surviving subjects tended to be higher in the acoramidis group than in the placebo

group. In view of the following points, however, the efficacy of acoramidis can be expected in this subgroup as well to a certain extent: (1) The number of patients with NYHA Class III enrolled in Study AG10-301 is limited, giving the investigation limitations; (2) the frequency of cardiovascular-related hospitalization in all the patients including those who died during the study was lower in the acoramidis group than in the placebo group; and (3) acoramidis was shown to stabilize TTR irrespective of severity of cardiac failure. Taking account of results of the subgroup analysis in Study AG10-301 and the points described below, however, the applicant should raise caution with a statement to the effect that the efficacy of acoramidis might be lower in patients with NYHA Class III than in those with NYHA Class I/II; and eligibility of such patients for acoramidis should be judged by physicians with a full understanding of the mechanism of action of acoramidis and clinical study results.

- In view of the mechanism of action of acoramidis, which prevents deposition of amyloid fibril in the cardiac muscle by stabilizing TTR tetramers, acoramidis may not exert the effect fully in patients with advanced disease accompanied by cardiac failure of high severity (NYHA Class).
- Tafamidis, which has the same mechanism of action as that of acoramidis, is shown to tend to have less efficacy in patients with NYHA Class III than in those with NYHA Class I/II.

Patients with NYHA Class IV were not included in Study AG10-301 or ALXN2060-TAC-302, and the efficacy and safety of acoramidis in this patient population remain unclear, but the efficacy is presumed to be further limited. However, the treatment option for ATTR-CM, a progressive disease, is limited to tafamidis that has the same mechanism of action as that of acoramidis, and cardiac failure is supposed to progress or be resolving in patients receiving acoramidis. Considering above, PMDA concluded that patients eligible for acoramidis might include those with NYHA Class IV, with the caution attached that the efficacy and safety have not been established in this patient population

Appropriateness of the above conclusion will be finalized, taking account of comments raised in the Expert Discussion.

7.R.3.4 Efficacy by disease type of ATTR-CM

The applicant's explanation about the effect of disease type of ATTR-CM on the efficacy of acoramidis:
Table 57 shows the results of all-cause mortality and the frequency of cardiovascular-related hospitalization, which are components of the primary endpoint in Part B of the foreign phase III study (Study AG10-301), by disease type. In both wild-type and variant subgroups, the results of all-cause mortality and the frequency of cardiovascular-related hospitalization favored acoramidis over placebo, and thus the efficacy of acoramidis can be expected in patients with either ATTRwt-CM or ATTRv-CM.

Table 57. All-cause mortality and frequency of cardiovascular-related hospitalization at up to Month 30 in Study AG10-301 by disease type (mITT)

	Wild type		Variant type	
	Placebo (n = 182)	Acoramidis (n = 370)	Placebo (n = 20)	Acoramidis (n = 39)
All-cause mortality (incidence % [number of subjects with the event])	22.5 (41)	18.4 (68)	55.0 (11)	28.2 (11)
Frequency of cardiovascular-related hospitalization in surviving subjects (times per year) (mean ± SD) (number of subjects with events/number of subjects analyzed)	0.28 ± 0.567 (46/141)	0.13 ± 0.322 (61/302)	0.52 ± 0.687 (4/9)	0.16 ± 0.366 (7/28)

In view of the applicant's explanation, PMDA concluded that the efficacy of acoramidis can be expected irrespective of disease type of ATTR-CM.

7.R.4 Safety

Based on adverse events in Japanese and foreign clinical studies and the review described below, and in view of the efficacy of acoramidis reviewed in Section "7.R.3 Efficacy," PMDA concluded that acoramidis has clinically acceptable safety in patients with ATTR-CM.

7.R.4.1 Incidences of adverse events in clinical studies

The applicant's explanation about the incidences of adverse events in clinical studies of acoramidis:

Table 58 shows summary of the safety in the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302). The incidence of adverse events did not differ between the dose groups in Study AG10-301. An adverse event of which the incidence was higher in the acoramidis group than in the placebo group in Study AG10-301 was COVID-19 (14.2% in the placebo group and 21.1% in the acoramidis group), but a causal relationship to the study drug was ruled out for the event in any subject. No remarkable difference was observed in the safety profile between the acoramidis group in Study AG10-301 and the patient population in Study ALXN2060-TAC-302, showing no increasing trend of a certain risk in Japanese patients.

Table 58. Incidence of adverse events in Studies AG10-301 and ALXN2060-TAC-302 (safety analysis set)

	Study AG10-301		Study ALXN2060-TAC-302 (n = 25)
	Placebo (n = 211)	Acoramidis (n = 421)	
All adverse events	97.6 (206)	98.1 (413)	100 (25)
Serious adverse events	64.9 (137)	54.6 (230)	48.0 (12)
Adverse events leading to death	17.1 (36)	14.3 (60)	0 (0)
Adverse events leading to discontinuation of the study drug	8.5 (18)	9.3 (39)	8.0 (2)
Adverse events for which a causal relationship to the study drug could not be ruled out	5.2 (11)	11.9 (50)	12.0 (3)

Incidence % (number of subjects)

In view of the applicant's explanation, PMDA concluded that no clinically relevant differences were observed in incidence of adverse events between dose groups in clinical studies or between patients in and outside Japan, but the adverse events of interest based on the incidence in clinical studies of acoramidis and the mechanism of action are continuously reviewed in the following sections.

7.R.4.2 Renal dysfunction

In the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302), renal dysfunction occurred in more than 1 subject as an adverse event for which a causal relationship to acoramidis could not be ruled out. PMDA asked the applicant to explain whether acoramidis might cause renal dysfunction or worsen renal impairment.

The applicant's explanation about an effect of acoramidis on renal functions:

Table 59 shows changes in eGFR from baseline over the study treatment period in Study AG10-301. In the placebo group, eGFR tended to decrease gradually over a period up to Month 30, while in the acoramidis group, a decrease in eGFR was observed on Day 28, and then the decreased eGFR was

maintained over a period up to Month 30. The decreasing trend in eGFR after the start of the acoramidis treatment was also observed in Study ALXN2060-TAC-302 (82.47 ± 23.134 mL/min/1.73 m^2 at baseline, changes in eGFR from baseline to Days 14 and 30 were −13.71 ± 7.283 mL/min/1.73 m^2 and −19.61 ± 12.294 mL/min/1.73 m^2, respectively). Results from Study AG10-201 (Table 60) showed that the decreased eGFR with acoramidis tended to be resolving after the end of the acoramidis treatment.

Table 59. Changes in eGFR from baseline over the study treatment period in Study AG10-301 (mL/min/1.73 m^2) (safety analysis set)

	Placebo	Acoramidis
Baseline	61.0 ± 18.67 (211)	60.9 ± 18.16 (421)
Change from baseline		
Day 28	-0.7 ± 7.28 (193)	-8.2 ± 9.39 (378)
Month 3	-1.5 ± 7.93 (194)	-7.1 ± 8.85 (372)
Month 6	-2.5 ± 9.57 (180)	-7.4 ± 9.51 (340)
Month 9	-2.7 ± 9.20 (171)	-7.5 ± 10.72 (332)
Month 12	-3.2 ± 10.06 (175)	-7.8 ± 10.81 (343)
Month 15	-4.3 ± 10.28 (170)	-8.3 ± 10.96 (323)
Month 18	-4.5 ± 10.52 (165)	-7.9 ± 10.50 (310)
Month 21	-6.1 ± 11.19 (159)	-8.7 ± 11.89 (301)
Month 24	-6.4 ± 12.32 (145)	-9.5 ± 11.30 (299)
Month 27	-6.5 ± 13.46 (133)	-8.6 ± 11.64 (287)
Month 30	-6.6 ± 14.14 (138)	-8.4 ± 11.74 (293)

Mean ± SD (number of subjects)

Table 60. Changes in eGFR from baseline over the study treatment period and after end of the treatment in Study AG10-201 (mL/min/1.73 m^2) (safety analysis set)

	Placebo	Acoramidis	
		400 mg	800 mg
Baseline	62.22 ± 15.403 (17)	54.28 ± 13.474 (16)	58.83 ± 15.665 (16)
Change from baseline			
Day 14	-0.08 ± 7.930 (17)	-2.66 ± 7.271 (16)	-4.56 ± 5.194 (16)
Day 28	4.66 ± 9.320 (17)	-2.80 ± 5.571 (16)	-6.31 ± 7.628 (16)
7-14 days after end of treatment	-0.48 ± 10.192 (17)	-1.88 ± 9.696 (16)	-0.79 ± 8.823 (15)

Mean ± SD (number of subjects)

In Studies AG10-301 and ALXN2060-TAC-302, the incidence of adverse events[58)] related to renal dysfunction was 33.6% (71 of 211 subjects) in the placebo group and 36.3% (153 of 421 subjects) in the acoramidis group in Study AG10-301 and 32.0% (8 of 25 subjects) in Study ALXN2060-TAC-302. In Study AG10-301, adverse events related to renal dysfunction leading to death occurred in 0.5% of subjects in the placebo group (1 subject, end stage renal disease) and 0.5% of subjects in the acoramidis group (2 subjects, chronic kidney disease and end stage renal disease in 1 subject each), but a causal relationship to the study drug was ruled out for all the events. In Study ALXN2060-TAC-302, no adverse events related to renal dysfunction leading to death occurred. Serious adverse events related to renal dysfunction occurred in 7.6% of subjects in the placebo group (16 subjects; acute kidney injury in 6 subjects; hypervolaemia in 3 subjects; nephropathy toxic in 2 subjects; acute kidney injury/hypervolaemia in 2 subjects; pericarditis, hyponatraemia, and end stage renal disease in 1 subject each) and 7.1% of subjects in the acoramidis group (30 subjects; acute kidney injury in 18 subjects; chronic kidney disease and blood creatinine increased in 2 subjects each; hypervolaemia/acute kidney injury/end stage renal disease, prerenal failure/renal dysfunction/hypervolaemia, acute kidney injury/renal dysfunction/normochromic normocytic anaemia, acute kidney injury/hypervolaemia, renal

[58)] MedDRA SMQ “Acute renal failure” [broad] and MedDRA SMQ “Chronic kidney disease” [broad]

dysfunction, hyperkalaemia, hypocalcaemia, and nephropathy toxic in 1 subject each) in Study AG10-301, but a causal relationship to the study drug was ruled out for all of the events. In Study ALXN2060-TAC-302, no serious adverse events related to renal dysfunction occurred. In Study AG10-301, adverse events related to renal dysfunction leading to discontinuation of the study drug did not occur in the placebo group but occurred in 1.2% of subjects in the acoramidis group (5 subjects; acute kidney injury in 2 subjects; chronic kidney disease, end stage renal disease, and hypocalcaemia in 1 subject each). A causal relationship to the study drug was ruled out for all of the events. Except for 2 subjects who experienced adverse events related to renal impairment leading to death (chronic kidney disease and end stage renal disease in 1 subject each), all recovered. In Study ALXN2060-TAC-302, an adverse event related to renal dysfunction leading to discontinuation of the study drug occurred in 4.0% of subjects (1 subject, renal dysfunction). A causal relationship to the study drug could not be ruled out for the event, but the event resolved after discontinuation of the study drug. Adverse events related to renal dysfunction for which a causal relationship to the study drug could not be ruled out occurred in 0.9% of subjects in the placebo group (2 subjects; renal failure and proteinuria in 1 subject each) and 1.7% of subjects in the acoramidis group (7 subjects; blood creatinine increased in 3 subjects; urine albumin/creatinine ratio increased and renal dysfunction in 2 subjects each) in Study AG10-301, and in 8.0% of subjects (2 subjects; renal dysfunction in 2 subjects) in Study ALXN2060-TAC-302. Except for severe proteinuria in the placebo group in Study AG10-301, all of these events were mild or moderate or Common Terminology Criteria for Adverse Event (CTCAE) Grade 1 or 2 in severity and considered potentially attributable to worsening of renal functions associated with underlying disease, comorbidities, and advanced age in the patients.

For the safety in patients with renal impairment, Table 61 shows the incidence of adverse events in Study AG10-301 by renal function. The incidence of adverse events including those related to renal dysfunction did not tend to be clearly higher in the population with eGFR <45 mL/min/1.73 m^2 than in those with eGFR ≥45 mL/min/1.73 m^2. In Study ALXN2060-TAC-302, patients with eGFR <45 mL/min/1.73 m^2 were not eventually enrolled.

Table 61. Incidence of adverse events in Study AG10-301 by renal function at baseline (safety analysis set)

	eGFR <45 mL/min/1.73 m^2		eGFR ≥45 mL/min/1.73 m^2	
	Placebo (n = 46)	Acoramidis (n = 90)	Placebo (n = 165)	Acoramidis (n = 331)
All adverse events	100 (46)	97.8 (88)	97.0 (160)	98.2 (325)
Serious adverse events	73.9 (34)	67.8 (61)	62.4 (103)	51.1 (169)
Adverse events leading to death	28.3 (13)	23.3 (21)	13.9 (23)	11.8 (39)
Adverse events leading to discontinuation of the study drug	10.9 (5)	13.3 (12)	7.9 (13)	8.2 (27)
Adverse events for which a causal relationship to the study drug could not be ruled out	6.5 (3)	13.3 (12)	4.8 (8)	11.5 (38)

Incidence % (number of subjects)

As shown above, a decrease in eGFR occurred relatively early after the start of acoramidis treatment, but it tended to resolve after the completion of acoramidis treatment, and the occurrence of renal dysfunction-associated adverse events shows no evident relationship between acoramidis and renal dysfunction. The applicant thus considers it unnecessary to raise caution in the package insert about decreased eGFR during acoramidis treatment.

PMDA's view:
The decreasing trend of eGFR was observed during acoramidis treatment. However, in view of the data on renal dysfunction-related adverse events and changes in eGFR during and after the completion of treatment, acoramidis is unlikely to cause clinically relevant renal dysfunction. Nevertheless, the degree of the decrease in eGFR after treatment is indicative of possible decrease in eGFR early after the start of acoramidis treatment. The necessity of periodical renal function test during treatment should be communicated through the package insert. Appropriateness of these conclusions will be finalized taking account of comments raised in the Expert Discussion.

7.R.4.3 Expected adverse events associated with acoramidis's mechanism of action

The applicant's explanation about likely adverse events due to stabilization effect on TTR tetramers, acoramidis's mechanism of action:
TTR is reported to transport and store T_4, enhance insulin secretion, and transport retinol-retinol-binding protein complex. The incidences of adverse events related to thyroid function, blood glucose as well as eye and skin in the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) were investigated.

(a) Effect on thyroid function
Adverse events related to thyroid dysfunction[59)] occurred in 3.8% (7 of 211) of subjects in the placebo group and 4.5% (18 of 421) of subjects in the acoramidis group in Study AG10-301 and in 4.0% (1 of 25) of subjects in Study ALXN2060-TAC-302, and all of them were mild or moderate in severity. No adverse events leading to death or adverse events leading to discontinuation of the study drug occurred. A serious adverse event occurred in 1 subject in the acoramidis group in Study AG10-301 (moderate hypothyroidism) but resolved before leading to discontinuation of the study drug, and its causal relationship to the study drug was ruled out. As shown above, the effect of acoramidis on thyroid function was not suggested, and the applicant considers it unnecessary to raise caution about adverse events related to thyroid dysfunction.

(b) Effect on blood glucose
For the effect of acoramidis on blood glucose, the incidences of adverse events related to hyperglycaemia/onset of diabetes mellitus[60)] and those related to hypoglycaemia[61)] were investigated. Adverse events related to hyperglycaemia/onset of diabetes mellitus occurred in 6.6% (14 of 211) of subjects in the placebo group and 3.8% (16 of 421) of subjects in the acoramidis group in Study AG10-301 and in 4.0% (1 of 25) of subjects in Study ALXN2060-TAC-302. Adverse events related to hypoglycaemia occurred in 0.9% (2 of 211) of subjects in the placebo group and 1.2% (5 of 421) of subjects in the acoramidis group in Study AG10-301, but no such events occurred in Study ALXN2060-TAC-302. Of either adverse events related to hyperglycaemia/onset of diabetes mellitus or those related to hypoglycaemia, none were identified as adverse events leading to death, serious adverse events, or adverse events leading to discontinuation of the study drug. All of the reported adverse events were mild or moderate in severity. As shown above, no effect raising safety problems was observed although some

59) MedDRA SMQ "Thyroid dysfunction" [broad]
60) MedDRA SMQ "Hyperglycaemia/new onset diabetes mellitus" [narrow]
61) MedDRA SMQ "Hypoglycaemia" [narrow], MedDRA PT "Blood glucose abnormal," MedDRA PT "Blood glucose fluctuation"

patients experienced adverse events related to blood glucose fluctuation. The applicant thus considers it unnecessary to raise caution about the effect on blood glucose.

(c) Eye disorder and skin disorder

After the start of acoramidis treatment, a decrease in retinol binding protein in serum was observed, and adverse events related to eye disorder and skin disorder associated with decreased transport of retinol are expected. Adverse events related to eye disorder[62)] occurred in 12.3% (26 of 211) of subjects in the placebo group and 10.9% (46 of 421) of subjects in the acoramidis group in Study AG10-301 and in 16.0% (4 of 25) of subjects in Study ALXN2060-TAC-302. No adverse events leading to death or adverse events leading to discontinuation of the study drug occurred. Serious adverse events occurred in 0.9% (2 of 211) of subjects in the placebo group (conjunctival haemorrhage and retinal artery occlusion in 1 subject each) and 0.2% (1 of 421) of subjects in the acoramidis group (macular hole) in Study AG10-301. Macular hole in the acoramidis group resolved while the study drug was being continued, and a causal relationship to the study drug was ruled out.

Adverse events related to skin disorder[63)] occurred in 25.1% (53 of 211) of subjects in the placebo group and 25.7% (108 of 421) of subjects in the acoramidis group in Study AG10-301 and in 28.0% (7 of 25) of subjects in Study ALXN2060-TAC-302. No adverse events leading to death occurred. Serious adverse events occurred in 1.2% (5 of 421) of subjects in the acoramidis group (eczema asteatotic/purpura senile, angioedema, drug eruption, skin ulcer, and telangiectasia in 1 subject each) in Study AG10-301, but for all of the events, the study drug was continued and a causal relationship to the study drug was ruled out. In addition, all of the events, except for skin ulcer, resolved. Adverse events leading to discontinuation of the study drug occurred in 0.2% (1 of 421) of subjects in the acoramidis group (rash erythematous) in Study AG10-301 and in 4.0% (1 of 25) of subjects (drug eruption) in Study ALXN2060-TAC-302, but both resolved after discontinuation of the study drug.

As shown above, the decrease in retinol binding protein in serum was observed, but no adverse events of eye disorder or skin disorder raising clinical concerns occurred. The applicant thus considers it unnecessary to raise caution about these adverse events.

PMDA has concluded that currently there are no safety concerns warranting caution in using acoramidis for the likely adverse events associated with its action mechanism mentioned in the above (a) to (c).

7.R.5 Intended population and indication

The applicant's explanation about the intended population and indication of acoramidis:

The foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) demonstrated the efficacy and safety of acoramidis in the target patient populations of these studies. Acoramidis must be used to patients who have received a diagnosis of transthyretin amyloid cardiomyopathy accompanied by cardiac failure as done in the above clinical studies. Patients with prior liver transplant were not eventually enrolled in either Study AG10-301 or ALXN2060-TAC-302, but in patients with prior liver transplant, ATTR-CM could progress with TTRwt being further depositing on

62) MedDRA SOC "Eye disorders"
63) MedDRA SOC "Skin and subcutaneous tissue disorders"

the existing amyloid deposit (*Biochem Biophys Res Commun.* 2000;274:702-6). In view of the mechanism of action of acoramidis, the efficacy can be expected even in patients with prior liver transplant. The applicant considers it acceptable to include the concerned patients in the intended population of acoramidis.

Accordingly, the applicant concluded that the package insert of acoramidis should provide the following information; the indication of "Transthyretin amyloid cardiomyopathy (wild-type and hereditary)," details of the patients enrolled in Studies AG10-301 and ALXN2060-TAC-302 in the Clinical Studies section, the statement in the Precautions Concerning Indication section that acoramidis be used in patients with cardiac failure accompanying transthyretin amyloid cardiomyopathy, and a cautionary note in the Clinical Studies section that eligible patients must be selected by physicians with a full understanding of the information presented and the inclusion criteria for the clinical studies.

PMDA's view:
The intended population of acoramidis should be patients with confirmed ATTR-CM according to the Guidelines on Diagnosis and Treatment of Cardiac Amyloidosis in Japan and findings of cardiac failure potentially attributable to cardiac amyloidosis. In view of the review in Section 7.R.3 Efficacy, patients with cardiac failure of NYHA Class III or greater and those with ATTR-CM irrespective of disease type may be included in the intended population of acoramidis. At the same time, caution should be raised about the use of acoramidis in patients with NYHA Class III or IV, as in Section "7.R.3.3 Efficacy by severity of cardiac failure." In view of the applicant's explanation, patients with prior liver transplant may be included in the intended population, but the package insert should note that there are no clinical study data or no efficacy and safety of acoramidis established. In conclusion, the indication of acoramidis and Precautions Concerning Indication should be described as follows. The appropriateness of these conclusions will be finalized taking account of comments raised in the Expert Discussion.

Indication
Transthyretin amyloid cardiomyopathy (wild-type and variant)

Precautions Concerning Indication
- Acoramidis should be administered to patient who have been confirmed to have received a definitive diagnosis of transthyretin amyloidosis with reference to the latest guideline.
- Acoramidis should be used in patients with cardiac failure accompanying transthyretin amyloid cardiomyopathy. Eligible patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and the inclusion criteria for the clinical studies.
- The efficacy of acoramidis may be lower in patients with NYHA Class III than in those with NYHA Class I or II. The necessity of acoramidis for patients with NYHA Class III should be judged based on a full understanding of the mechanism of action of acoramidis and a relationship between NYHA Class and efficacy suggested in the clinical studies, with due consideration of the patient's condition.
- The efficacy and safety of acoramidis in patients with NYHA Class IV have not been established.
- The efficacy and safety of acoramidis in patients with prior liver transplant have not been established.

7.R.6 Dosage and administration

The dosage regimen used in the foreign phase III study (Study AG10-301) and Japanese phase III study (Study ALXN2060-TAC-302) was specified based on the investigation results in terms of PK and PD [see Section "6.R.2 Appropriateness of proposed dosage and administration"]. Studies AG10-301 and ALXN2060-TAC-302 with the concerned dosage regimen demonstrated the efficacy and safety [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. In view of the above result, PMDA concluded that the dosage and administration of acoramidis should be twice-daily oral administration of acoramidis 800 mg, the same dosage regimen as that used in Studies AG10-301 and ALXN2060-TAC-302.

7.R.7 Post-marketing investigations

In the present application, the applicant does not plan additional pharmacovigilance activities other than early post-marketing phase vigilance. For the post-marketing investigations of acoramidis, there are no items to be investigated at the post-marketing surveillance in addition to information gathered during early post-marketing phase vigilance and regular pharmacovigilance activities at present. taking account of the following points. PMDA considers the following applicant's policy acceptable; The applicant plans to conduct early post-marketing phase vigilance and regular pharmacovigilance activities of acoramidis but does not plan to conduct post-marketing surveillance.

- In Japan, a TTR stabilizer indicated for ATTR-CM has been already approved, and its use results indicate no clear concerns in the safety profile of the TTR stabilizer.
- For the safety of acoramidis, adverse events in the Japanese and foreign phase III studies (Studies AG10-301 and ALXN2060-TAC-302) have raised no additional concerns compared with the safety profile of the approved TTR stabilizer, except for a decrease in eGFR, which may occur after the start of acoramidis treatment but can be managed by periodic tests [see Section "7.R.4 Safety"].

The applicant, however, is required to consider conducting post-marketing surveillance as an additional pharmacovigilance activity when a new item to be investigated is identified after the market launch of acoramidis.

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 5.3.5.2-1) 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 acoramidis has efficacy in the treatment of transthyretin amyloid cardiomyopathy (wild-type and variant), and that acoramidis has acceptable safety in view of its benefits. Neither the drug product nor its drug substance is classified as a poisonous drug or powerful drug. Acoramidis is clinically meaningful because it offers a new treatment option for patients with transthyretin amyloid cardiomyopathy (wild-type and variant). Efficacy, intended population of acoramidis, cautionary notes in the package insert, and post-marketing investigations are subject to further discussion.

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

Review Report (2)

February 13, 2025

Product Submitted for Approval

Brand Name	Beyonttra Tablets 400 mg
Non-proprietary Name	Acoramidis Hydrochloride
Applicant	Alexion Pharma GK
Date of Application	April 17, 2024

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 conclusions on clinical positioning of acoramidis, usability of foreign clinical study data, efficacy, intended population and indication, dosage and administration, and post-marketing investigations presented in the Review Report (1).

1.1 Safety

In the Review Report (1), PMDA has concluded that the incidences of adverse events reported from the clinical studies are not indicative of clinically problematic differences between treatment groups or Japanese and non-Japanese patients (Section "7.R.4.1 Adverse events in clinical studies"), and that there are no current safety concerns warranting cautious use of acoramidis in terms of its action mechanism-associated potential adverse events (Section "7.R.4.3 Expected adverse events associated with acoramidis's mechanism of action"). The expert advisors supported these conclusions.

A risk of renal dysfunction during acoramidis treatment was investigated as follows. The investigation was based on data additionally submitted, which include changes in eGFR from baseline (Table 62) and incidences of adverse events related to renal dysfunction[58)] (Table 63) by renal function (eGFR <45 mL/min/1.73 m^2 or ≥45 mL/min/1.73 m^2) in the foreign phase III study (Study AG10-301).

Table 62. Changes in eGFR from baseline over the study treatment period in Study AG10-301 by baseline renal function (mL/min/1.73 m^2) (safety analysis set)

	eGFR <45 mL/min/1.73 m^2		eGFR ≥45 mL/min/1.73 m^2	
	Placebo	Acoramidis	Placebo	Acoramidis
Baseline	36.3 ± 6.59 (46)	37.4 ± 6.37 (90)	67.9 ± 14.69 (165)	67.3 ± 14.71 (331)
Change from baseline				
Day 28	0.8 ± 5.96 (43)	-5.7 ± 7.18 (82)	-1.2 ± 7.58 (150)	-8.8 ± 9.83 (296)
Month 3	0.5 ± 6.36 (42)	-3.6 ± 7.17 (77)	-2.0 ± 8.24 (152)	-8.0 ± 9.03 (295)
Month 6	0.9 ± 7.82 (36)	-3.2 ± 6.68 (65)	-3.4 ± 9.80 (144)	-8.3 ± 9.82 (275)
Month 9	0.5 ± 8.86 (38)	-2.4 ± 7.68 (61)	-3.7 ± 9.12 (133)	-8.7 ± 10.99 (271)
Month 12	1.6 ± 9.61 (36)	-2.5 ± 7.31 (68)	-4.4 ± 9.84 (139)	-9.1 ± 11.14 (275)
Month 15	0.7 ± 7.91 (36)	-3.1 ± 7.25 (59)	-5.7 ± 10.44 (134)	-9.4 ± 11.32 (264)
Month 18	1.7 ± 9.01 (34)	-3.4 ± 7.56 (60)	-6.1 ± 10.31 (131)	-9.0 ± 10.83 (250)
Month 21	0.4 ± 10.45 (30)	-4.4 ± 7.86 (56)	-7.6 ± 10.85 (129)	-9.6 ± 12.44 (245)
Month 24	1.6 ± 10.01 (27)	-5.4 ± 6.37 (52)	-8.2 ± 12.12 (118)	-10.4 ± 11.92 (247)
Month 27	1.6 ± 11.08 (25)	-4.3 ± 7.26 (48)	-8.4 ± 13.30 (108)	-9.5 ± 12.17 (239)
Month 30	2.5 ± 12.60 (25)	-4.4 ± 8.86 (50)	-8.6 ± 13.71 (113)	-9.3 ± 12.10 (243)

Mean ± SD (number of subjects)

Table 63. Incidence of adverse events related to renal dysfunction in Study AG10-301 by baseline renal function (safety analysis set)

	eGFR <45 mL/min/1.73 m^2		eGFR ≥45 mL/min/1.73 m^2	
	Placebo (n = 46)	Acoramidis (n = 90)	Placebo (n = 165)	Acoramidis (n = 331)
All adverse events	43.5 (20)	56.7 (51)	30.9 (51)	30.8 (102)
Serious adverse events	8.7 (4)	20.0 (18)	7.3 (12)	3.6 (12)
Adverse events leading to death	0 (0)	1.1 (1)	0.6 (1)	0.3 (1)
Adverse events leading to discontinuation of the study drug	0 (0)	3.3 (3)	0 (0)	0.6 (2)
Adverse events for which a causal relationship to the study drug could not be ruled out	2.2 (1)	1.1 (1)	0.6 (1)	1.8 (6)

Incidence % (number of subjects)

In patients in the acoramidis group with eGFR <45 mL/min/1.73 m^2, eGFR decreased on Day 28. The extent of decrease was, however, smaller than that in patients in the acoramidis group with eGFR ≥45 mL/min/1.73 m^2, and it tended to recover over Month 12. In patients in the acoramidis group with eGFR <45 mL/min/1.73 m^2, the incidences of renal dysfunction-associated serious adverse events tended to be higher than in those in the placebo group and in the acoramidis group with eGFR ≥45 mL/min/1.73 m^2, but a causal relationship to the study drug was ruled out for all these events.

Based on the incidences of renal dysfunction-associated adverse events and over-time change in eGFR by baseline renal function, the use of acoramidis in patients with severe renal impairment is acceptable, which however warrants careful attention to potential progression of renal impairment in view of the following. Such cautionary note should be added in the package insert.

- The mechanism of decrease in eGFR after acoramidis administration has yet to be elucidated.
- Study AG10-301 excluded patients with eGFR <15 mL/min/1.73 m^2. Experience with acoramidis is limited in patients with eGFR 15 to 30 mL/min/1.73 m^2.

As in Section "7.R.4.2 Renal dysfunction" in the Review Report (1), PMDA has concluded that the necessity of periodical renal function test for patients on acoramidis should be communicated through the package insert. At the Expert Discussion, the expert advisors supported this conclusion and the above-mentioned conclusion as well.

1.2 Risk management plan (draft)

In view of the discussions in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and the comments at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for acoramidis should include the safety specification presented in Table 64, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 65.

Table 64. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Drug-drug interactions with substrates of CYP2C8, CYP2C9, or OATP1B1	None
Efficacy specification		
None		

Table 65. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Disseminate data gathered during early post-marketing phase vigilance

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 condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years.

Indication

Transthyretin amyloid cardiomyopathy (wild-type and variant)

Dosage and Administration

The usual adult dosage is 800 mg of acoramidis hydrochloride administered orally twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

A→B	Apical-to-basolateral
A/G ratio	Albumin/globulin ratio
Acoramidis	Acoramidis hydrochloride
AL	Amyloid light-chain
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATTR-CM	Transthyretin amyloid cardiomyopathy
AUC	Area under the plasma concentration-time curve
AUC_{ss}	AUC at steady state
AUC_{tau}	AUC from administration to the end of the dosing interval
AUC_{0-t}	AUC from administration to the time of last measured concentration
AUC_{0-12h}	AUC from administration to 12 hours
AUC_{0-24h}	AUC from administration to 24 hours
AUC_{0-48h}	AUC from administration to 48 hours
$AUC_{0-\infty}$	AUC from administration extrapolated to infinity
BA	Bioavailability
B→A	Basolateral-to-apical
BCRP	Breast cancer resistance protein
Beyonttra	Beyonttra Tablets 400 mg
BMI	Body mass index
BSEP	Bile salt export pump
BUN	Blood urea nitrogen
CCK-8	Cholecystokinin octapeptide
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
$C_{min,ss}$	Minimum plasma concentration at steady state
CI	Confidence interval
CL	Total body clearance
CL/F	Apparent total body clearance
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical quality attribute
CrCL	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid
D1	Zero-order absorption duration
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FITC	Fluoresceinisothiocyanate
FPE	Fluorescent probe exclusion
GC	Gas chromatography
GLP	Good Laboratory Practice
[redacted]PE	[redacted] polyethylene
HEK	Human embryonic kidney
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
hERG	Human ether-à-go-go related gene

HMDP/HDP	Hydroxymethylene diphosphonate
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HPLC	High performance liquid chromatography
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PFSB/ELD Notification No. 1216001 dated December 16, 2002) and "Partial Revision of the Guideline on Impurities in New Drug Substances" (PFSB/ELD Notification No. 1204001 dated December 4, 2006)
IC_{50}	50% inhibitory concentration
IgG	Immunoglobulin G
IR	Infrared absorption spectroscopy
ITT	Intent-to-treat
K_a	First-order absorption rate constant
K_{app}	Apparent dissociation constant
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Summary
K_d	Dissociation constant
K_I	Concentration of the inhibitor that yields 50% of the maximum inactivation rate
k_{inact}	Maximum inactivation rate constant
k_{on}	Dissociation rate constant
k_{off}	Association rate constant
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
[redacted]PE	[redacted] polyethylene
Lys	Lysine
MAD	Multiple ascending dose
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MDCK	Madin-Darby canine kidney
mITT	Modified intent-to-treat
MMRM	Mixed models repeated measures
MPP^+	1-Methyl-4-phenylpyridinium
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectroscopy
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app}	Apparent permeability coefficient
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred terms
PTP	Press through pack
PVC	Polyvinyl chloride

Q/F	Apparent inter-compartment clearance
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RH	Relative humidity
SD	Sprague-Dawley
Ser	Serine
SMQ	Standardised MedDRA queries
SOC	System organ class
Tafamidis	Tafamidis meglumine and tafamidis
t_{max}	Time to maximum plasma concentration
TTR	Transthyretin
$t_{1/2}$	Elimination half-life
T_4	Thyroxine
UGT	Uridine diphosphate-glucuronosyltransferase
ULN	Upper limit of normal
UV-A	Ultraviolet A
UV-B	Ultraviolet B
UV/VIS	Ultraviolet-visible spectrophotometry
V_{ss}	Volume of distribution at steady state
V_c/F	Apparent central volume of distribution
V_p/F	Apparent peripheral volume of distribution
WB	Western blot