Report on the Deliberation Results

February 26, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Vyndaqel Capsules 20 mg
Non-proprietary Name	Tafamidis Meglumine (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	November 2, 2018

Results of Deliberation

In its meeting held on February 21, 2019, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Due to very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are accumulated, to understand the characteristics of patients treated with the product and promptly collect the safety and efficacy data of the product, so as to take necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 12, 2019
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	Vyndaqel Capsules 20 mg
Non-proprietary Name	Tafamidis Meglumine
Applicant	Pfizer Japan Inc.
Date of Application	November 2, 2018
Dosage Form/Strength	Capsules each containing 20 mg of Tafamidis Meglumine
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 414 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0524-1 dated May 24, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 3 of 2018 [*30 yaku*]; Administrative notice dated March 27, 2018); the product underwent SAKIGAKE comprehensive evaluation consultation for drugs.
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 for the treatment of transthyretin amyloid cardiomyopathy (wild-type or 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 shown below, with the following conditions. The occurrence of hepatic disorders, hypersensitivity reactions, infections, and other events and safety in patients with variant ATTR-CM should be further investigated.

Indications	Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy <u>Transthyretin amyloid cardiomyopathy (wild-type or variant)</u>

(Underline denotes additions.)

Dosage and Administration

Transthyretin familial amyloid polyneuropathy

The usual adult dose is 20 mg of Tafamidis Meglumine administered orally once daily.

Transthyretin amyloid cardiomyopathy

The usual adult dose is 80 mg of Tafamidis Meglumine administered orally once daily. The dose may be reduced depending on tolerability.

(Underline denotes additions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Due to very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are accumulated, to understand the characteristics of patients treated with the product and promptly collect the safety and efficacy data of the product, so as to take necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

December 21, 2018

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	Vyndaqel Capsules 20 mg
Non-proprietary Name	Tafamidis Meglumine
Applicant	Pfizer Japan Inc.
Date of Application	November 2, 2018
Dosage Form/Strength	Capsules each containing 20 mg of Tafamidis Meglumine
Proposed Indication(s)	Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy Reductions in all-cause mortality and the frequency of cardiovascular-related hospitalizations in patients with transthyretin amyloid cardiomyopathy (wild-type or variant) (Underline denotes additions.)
Proposed Dosage and Administration	Transthyretin familial amyloid polyneuropathy The usual adult dose is 20 mg of Tafamidis Meglumine administered orally once daily. Transthyretin amyloid cardiomyopathy The usual adult dose is 80 mg of Tafamidis Meglumine administered orally once daily. (Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Vyndaqel is a capsule product containing Tafamidis Meglumine (tafamidis) as the active ingredient, developed by FoldRx Pharmaceuticals (currently, Pfizer Inc.). Tafamidis binds to tetrameric transthyretin (TTR), which transports thyroxine (T_4) and retinol-retinol-binding protein complex in the body, and inhibits (by stabilization) dissociation of the tetramer into monomers, thereby preventing the degeneration of TTR and the formation of insoluble fibrillar proteins (amyloid fibrils). In Japan, tafamidis was approved for "delay of peripheral neurologic impairment in patients with TTR familial amyloid polyneuropathy," in September 2013. In Europe, tafamidis was approved for "the treatment of TTR amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment" in November 2011. As of November 2018, tafamidis has been approved in 41 countries.

Similarly to TTR familial amyloid polyneuropathy (ATTR-PN), TTR amyloid cardiomyopathy (ATTR-CM) is a type of amyloidosis caused by the tissue deposition of TTR-derived amyloid. In patients with ATTR-CM, amyloid is deposited predominantly in the myocardia, resulting in a disturbance of cardiac function. TTR is known to be categorized into 2 types: wild-type TTR with the normal amino acid sequence and variant TTR which promotes fibrillogenesis. Regardless of the presence of a TTR gene mutation, ATTR-CM is manifested by typical symptoms of restrictive heart diseases and conduction abnormalities such as bundle branch block, atrioventricular block, and atrial fibrillation. ATTR-CM is generally associated with a poor prognosis, and most patients suffer sudden cardiac death or fatal events such as congestive cardiac failure and myocardial infarction (*Am J Med.* 1996;101:395-400 and *Mayo Clin Proc.* 1984;59:547-55).

The applicant, concluding that the clinical studies have demonstrated the efficacy and safety of tafamidis in "reducing all-cause mortality and the frequency of cardiovascular-related hospitalizations in patients with ATTR-CM (wild-type or variant)," has recently filed a partial change approval application for tafamidis. In the US, an application was filed for the same indication in [redacted], 20[redacted]. However, as of November 2018, tafamidis has not been approved for this indication in any countries or regions outside Japan.

Tafamidis was designated as a SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 3 of 2018 [*30 yaku*]) on March 27, 2018, and as an orphan drug (Drug Designation No. 414 of 2018 [*30 yaku*]) on May 24, 2018, with the intended indication of "ATTR-CM."

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no additional data relating to the quality of tafamidis were submitted.

2.R Outline of the review conducted by PMDA

2.R.1 Novel excipients

Sorbitan monooleate is the excipient of the drug product. In the present application, its maximum daily dose is [redacted] mg, and it exceeds that of oral excipients of existing pharmaceutical products. Therefore, sorbitan monooleate is regarded as a novel excipient.

2.R.1.1 Safety

Based on the data submitted, PMDA has concluded that there is no specific safety problem with the daily dose of the novel excipient (sorbitan monooleate).

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

Although the present application is for a new indication and a new dosage, no new data on nonclinical pharmacology were submitted because the non-clinical pharmacology of tafamidis had been evaluated during the review process for initial approval.

3.R Outline of the review conducted by PMDA

PMDA's view:

The results of *in vitro* studies submitted for the initial approval for the treatment of ATTR-PN have shown that tafamidis binds to and stabilizes a wild-type or variant TTR tetramer, thereby inhibiting dissociation of the tetramer and the subsequent formation of TTR amyloid (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013). ATTR-CM is caused by the tissue deposition of TTR amyloid as with ATTR-PN, and tafamidis is expected to exert its efficacy in the treatment of ATTR-CM via the same mechanism of action. More than 60 TTR variants have been reported to be associated with cardiac symptoms (Clinical Practice Guidelines for Amyloidosis). However, the *in vitro* studies submitted for the initial approval investigated only 28 variants (including those that have not been shown to be associated with cardiac symptoms), and 1 (P24S) of these 28 variants was not stabilized by tafamidis (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013). Therefore, whether tafamidis has promising efficacy regardless of TTR mutant genotype should also be investigated based on results from clinical studies [see Section "7.R.2.3 Efficacy by ATTR-CM disease type or TTR genotype"].

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

Although the present application is for a new indication and a new dosage, no new data on nonclinical pharmacokinetics (PK) were submitted because the non-clinical PK of tafamidis had been evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity data submitted for the present application include the results of a carcinogenicity study and other toxicity studies (an immunotoxicity study and a genotoxicity study of impurities).

5.1 Carcinogenicity

A carcinogenicity study was conducted in rats. The results suggested that tafamidis had no carcinogenic potential (Table 1).

Table 1. Carcinogenicity study

Test system	Route of administration	Treatment duration	Major lesions	Dose	(mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached CTD
					0 [a]	0 [b]	3	10	30		
				N	70/sex	70/sex	60/sex	60/sex	70/sex		
Male and female rats (SD)	Oral	2 years (once daily)	Neoplastic lesions		None					30	4.2.3.4.1.1
			Non-neoplastic lesions		Hepatocellular hypertrophy, liver multinucleated giant cells, foci of clear cells, hepatocellular necrosis, and pigmented Kupffer cells						

a, Ultrapure water
b, 7.5% Vitamin E d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS)

5.2 Other studies

5.2.1 Immunotoxicity study

A T-cell dependent antibody response (TDAR) study was conducted in mice, and the results indicated no tafamidis-related changes in IgM or IgG response against keyhole limpet hemocyanin (KLH) (Table 2).

Table 2. Immunotoxicity study

Test system	Test method	Main findings	Attached CTD
Male and female mice (CByB6F1)	Tafamidis 0[a], 10, 30, or 120 mg/kg/day was orally administered to mice once daily for 28 days. KLH was intraperitoneally administered on Day 15 of treatment and Day 15 of a 4-week washout.	Death: 1[b] of 12 females at 10 mg/kg/day, 1[b] of 12 females at 30 mg/kg/day, and 2[c] of 24 males and 1[d] of 24 females at 120 mg/kg/day Other findings (at 120 mg/kg/day: decreased red blood cell count (males and females), decreased hemoglobin concentration (males), decreased white blood cell count, decreased lymphocyte count, and decreased eosinophil count (females)	4.2.3.7.2.2

a, 7.5% Vitamin E TPGS
b, The death was considered a change due to a dosing error.
c, The causes of death were considered unknown.
d, The death was considered due to urinary tract obstruction.

5.2.2 Toxicity studies of impurities

Reverse mutation tests were performed on Related Substances A and B. Both are impurities that may be present in the drug substance or drug product of Vyndaqel. The results indicated that neither of the impurities are mutagenic (Table 3).

Table 3. Genotoxicity studies of impurities

Test substance	Type of study		Test system	Metabolic activation (S9 treatment)	Concentration (μg/plate)	Test results	Attached CTD
Related Substance A	*in vitro*	Bacterial reverse mutation assay (Ames test)	Salmonella typhimurium: TA1535, TA1537, TA98	−/+	0[a], 5.4 to 1600	Negative	4.2.3.7.6.1
			Salmonella typhimurium: TA1535, TA1537, TA98, TA100	−/+	0[a], 5.4 to 5000	Negative[c]	
			Escherichia coli: WP2*uvrA*				
			Salmonella typhimurium: TA1535, TA1537, TA100	−/+	TA1535, TA1537: 0[a], 52 to 5000 TA100: 0[a], 17 to 5000	Negative[c]	
Related Substance A	*in vitro*	Bacterial reverse mutation assay (Ames test)	Salmonella typhimurium: TA100	−/+	0[b], 17 to 5000	Negative	4.2.3.7.6.2
Related Substance B	*in vitro*	Bacterial reverse mutation assay (Ames test)	Salmonella typhimurium: TA1535, TA1537, TA 98, TA100	−/+	0[a], 33 to 3330	Negative	4.2.3.7.6.3
			Escherichia coli: WP2*uvrA*				

a, DMSO
b, Acetone
c, In the culture of TA100, the number of revertant colonies in the tafamidis group increased to ≤1.8-fold that in the vehicle control group. Although this result did not meet the criteria for a positive response, a confirmatory assay using TA100 was repeated (CTD 4.2.3.7.6.2).

5.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA has concluded that the non-clinical toxicity evaluation identified no concerns for the clinical use of tafamidis.

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 the mean or mean ± standard deviation (SD).

6.1 Summary of biopharmaceutic studies and associated analytical methods

A liquid oral formulation of tafamidis was used in a foreign phase I study (Study B3461040) and a QT evaluation study (Study B3461031) in healthy adults, while the commercial formulation in Japan was used in a foreign phase I study (Study B3461056[1)]) in healthy adults as well as a foreign phase II study (Study B3461025) and a global phase III study (Study B3461028) in patients with ATTR-CM.

Plasma tafamidis concentrations were measured via liquid chromatography and tandem mass spectrometry (LC-MS/MS). The lower limit of quantification was 10.0 ng/mL in Study B3461056 and 3.00 ng/mL in other studies. The stability of TTR in plasma was assessed via immunoturbidimetry.

[1)] A 2-group, 2-period crossover study was conducted in 30 non-Japanese healthy adults to compare the pharmacokinetics (PK) of tafamidis following the administration of Vyndaqel (tafamidis meglumine) 80 mg and that following the administration of 61 mg of tafamidis (free acid) preparation. In this review report, the PK and safety data refer to those of Vyndaqel (tafamidis meglumine) 80 mg administered once daily for 7 days.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biomaterials

6.2.1.1 Enzyme inhibition (CTD 4.2.2.6.2)

Using human liver microsomes and uridine 5'-diphospho-glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7), the potency of tafamidis 1 to 100 μmol/L (final concentrations) in inhibiting the metabolism of substrates for these UGT isoforms was assessed, with or without 2% bovine serum albumin (BSA). When tested without 2% BSA, tafamidis inhibited the activity of UGT1A1, UGT1A4, and UGT2B7, with IC_{50} values of 30, 86, and 83 μmol/L, respectively. The IC_{50} values of tafamidis for other UGT isoforms were >100 μmol/L. When tested with 2% BSA, the IC_{50} values of tafamidis for all UGT isoforms were >100 μmol/L.

6.2.1.2 Enzyme induction (CTD 4.2.2.6.1)

Using primary human hepatocytes (3 lots), the potency of tafamidis 0.03 to 50 μmol/L (final concentrations) in inducing Messenger ribonucleic acid (mRNA) expression and enzyme activity of cytochrome P450 (CYP) 1A2, CYP2B6, and CYP3A4 was assessed. Although tafamidis did not induce the mRNA expression or enzyme activity of CYP1A2, it induced both the mRNA expression and enzyme activity of CYP2B6, and also induced the mRNA expression of CYP3A4 in a concentration-dependent manner. The EC_{50} and E_{max} values of tafamidis were from 20 to 29 μmol/L and 5.9 to 11, respectively for induction of the mRNA expression of CYP2B6, and 28 μmol/L and 5.8 for that of CYP3A4.

6.2.1.3 Transporter studies (CTD 4.2.2.6.3 to 8)

When tafamidis 0.1 to 10 μmol/L (final concentrations) was added to HEK293 cells expressing organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, the intracellular uptake of tafamidis was comparable to the uptake into control cells, over the tested concentration range.

In Caco-2 cells, the potency of tafamidis 0.1 to 100 μmol/L (final concentrations) in inhibiting the P-glycoprotein (P-gp)-mediated transport of ^{3}H-digoxin was assessed. The IC_{50} value was >100 μmol/L.

In MDCKII cells expressing breast cancer resistance protein (BCRP), the potency of tafamidis 0.1 to 100 μmol/L (final concentrations) in inhibiting the BCRP-mediated transport of ^{3}H-labeled prazosin was assessed. The IC_{50} value was 1.16 μmol/L.

In CHO cells expressing organic anion transporter (OAT) 1 or organic cation transporter (OCT) 2, as well as HEK 293 cells expressing OAT3, the potency of tafamidis 0.1 to 100 μmol/L (final concentrations) in inhibiting the transport of their substrates was assessed. The IC_{50} values of tafamidis were 2.9 μmol/L for OAT1, 2.36 μmol/L for OAT3, and >100 μmol/L for OCT2.

In HEK293 cells expressing multidrug and toxin extrusion protein (MATE) 1 or MATE2-K, the potency of tafamidis 0.4 to 300 μmol/L (final concentrations) in inhibiting the transport of ^{14}C-labeled metformin, a

substrate for MATE1 or MATE2-K, was assessed. The IC_{50} value of tafamidis was 289.8 μmol/L for MATE2-K and >300 μmol/L for MATE1.

In HEK293 cells expressing OATP1B1 or OATP1B3, the potency of tafamidis 0.1 to 300 μmol/L (final concentrations) in inhibiting the transport of their substrates was assessed. The IC_{50} values of tafamidis were 31.0 μmol/L for OATP1B1 and >100 μmol/L for OATP1B3.

6.2.2 Studies in healthy adults

6.2.2.1 Single dose study in non-Japanese population (Study B3461040, CTD 5.3.3.1.2)

Table 4 shows the plasma pharmacokinetic (PK) parameters of tafamidis administered to 9 non-Japanese healthy adult men as a single oral dose of 240, 350, or 480 mg. The relationship between TTR percent stabilization[2)] and the plasma TTR/tafamidis molar ratio is shown in Figure 1.

Table 4. Plasma PK parameters of tafamidis following a single oral dose

Dose (mg)		N	C_{max} (μg/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)
240		6	14.33 ± 2.58	1.76	578.3 ± 49.4 [b]	47.85 ± 6.56 [b]
350		5	17.78 ± 3.07	2.00	758.7 ± 93.6 [c]	42.80 ± 3.70 [c]
480		5	22.50 ± 4.97	3.10	947.3 ± 102.2 [b]	41.10 ± 7.32 [b]

a, Median
b, N = 4
c, N = 3

[2)] Using immunoturbidimetry, the fraction of initial (FOI) tetramers (i.e., the proportion of remaining TTR tetramers) was calculated based on the plasma TTR tetramer concentrations before and after incubation under urea denaturing conditions, using the first formula below. In addition, as a quantitative measure of the inhibition of TTR tetramer dissociation, the percent stabilization (%) was calculated based on the FOI before and after the administration of tafamidis, using the second formula below.
FOI = [TTR tetramer concentration after incubation]/[initial TTR tetramer concentration]
Percent stabilization = [(average FOI after administration of tafamidis - average FOI before administration of tafamidis)/average FOI before administration of tafamidis] × 100

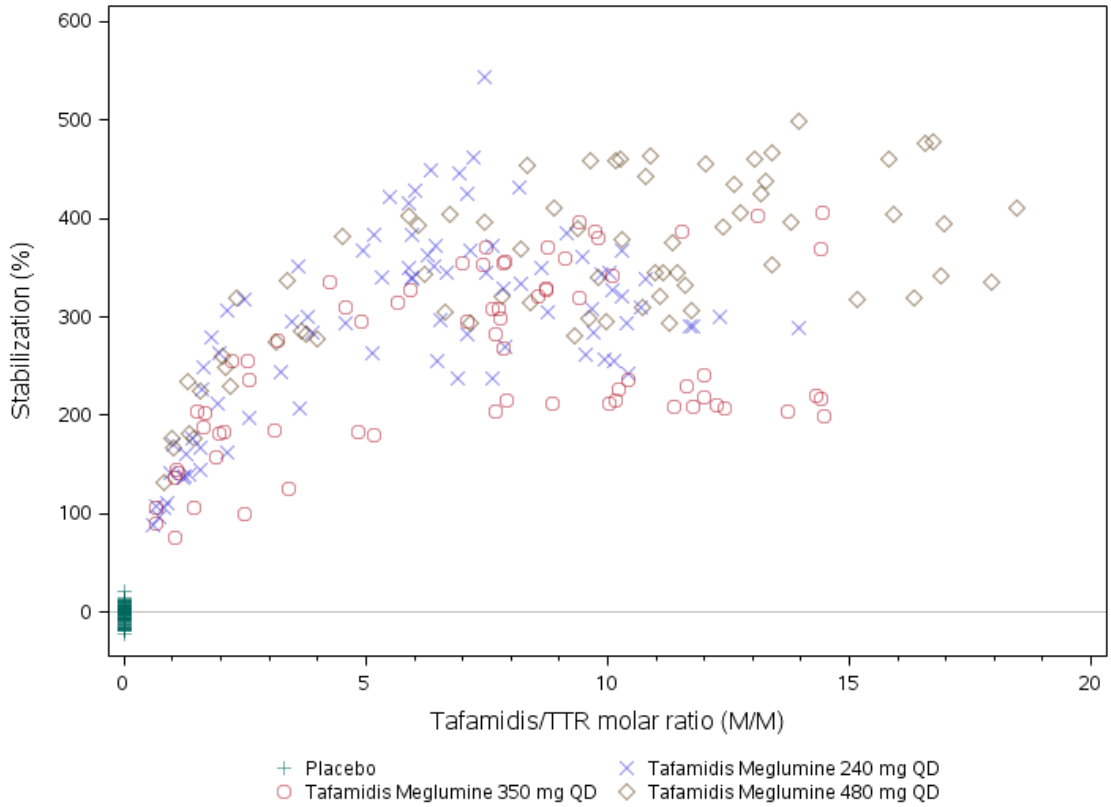

Figure 1. Relationship between TTR percent stabilization and plasma tafamidis/TTR molar ratio

6.2.2.2 Multiple dose study in non-Japanese healthy adults (Study B3461056, CTD 5.3.3.1.3)

Table 5 shows the plasma PK parameters of multiple oral doses of tafamidis 80 mg administered to 30 non-Japanese healthy adult men at once daily for 7 days.

Table 5. Plasma PK parameters of multiple oral doses of tafamidis

Dose (mg)	N	Time point (Day)	C_{max} (μg/mL)	t_{max}[a] (h)	AUC_{τ} (μg·h/mL)
80	30	7	9.241 ± 1.796	2.00	169.600 ± 35.637

a, Median

6.2.3 Patient studies

6.2.3.1 Global phase III study in patients with ATTR-CM (Study B3461028, CTD 5.3.5.1.1)

Tables 6 and 7 show plasma tafamidis concentrations and TTR percent stabilization of multiple doses of tafamidis 20 or 80 mg administered orally once daily to 264 Japanese or non-Japanese patients with wild-type or variant ATTR-CM .

Table 6. Plasma tafamidis concentrations following multiple oral doses (μg/mL)

Dose (mg)	Time point					
	Month 1 (trough)	Month 1 (4.5 hours post-dose)	Month 6 (9.5 hours post-dose)	Month 12 (9.5 hours post-dose)	Month 18 (1.5 hours post-dose)	Month 24 (1.5 hours post-dose)
20	2.257 ± 0.926 (86)	2.915 ± 1.004 (85)	3.052 ± 1.355 (78)	3.378 ± 1.356 (72)	3.012 ± 1.390 (67)	3.167 ± 1.536 (61)
80	8.388 ± 3.971 (170)	11.63 ± 4.56 (169)	12.25 ± 5.69 (160)	12.84 ± 6.14 (147)	12.47 ± 6.99 (132)	11.67 ± 5.88 (119)

Mean ± SD (N)

Table 7. TTR percent stabilization following multiple oral doses of tafamidis (%)

Dose (mg)	Time point					
	Month 1 (trough)	Month 1 (4.5 hours post-dose)	Month 6 (9.5 hours post-dose)	Month 12 (9.5 hours post-dose)	Month 18 (1.5 hours post-dose)	Month 24 (1.5 hours post-dose)
Placebo	3.4 ± 16.3 (153)	3.8 ± 15.4 (151)	4.7 ± 19.9 (137)	8.1 ± 23.8 (113)	9.6 ± 42.4 (99)	13.2 ± 55.3 (76)
20	145.9 ± 78.0 (75)	186.0 ± 89.4 (75)	174.9 ± 87.7 (69)	176.6 ± 72.7 (59)	150.0 ± 77.2 (58)	146.7 ± 86.3 (55)
80	243.8 ± 113.3 (150)	263.0 ± 122.8 (149)	246.7 ± 118.5 (142)	242.9 ± 110.2 (125)	241.1 ± 121.3 (115)	231.6 ± 108.8 (106)

Mean ± SD (N)

6.2.4 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

A population pharmacokinetic (PPK) analysis (NONMEM, Ver. 7.4) was performed based on plasma tafamidis concentration data (11,472 time points; 760 subjects) from foreign and Japanese clinical studies in patients with ATTR-CM (Studies B3461025 and B3461028) and other clinical studies.[3)] The plasma PK of tafamidis were described by a 2-compartment model with first-order absorption and elimination, and an absorption time lag. Candidate covariates influencing the plasma PK parameters of tafamidis were body weight for CL/F, V_c/F, V_p/F, and Q/F, formulation types and food for ka, and formulation types for bioavailability (F), and they were incorporated in a base model for assessment. Based on the results,[4)] age and moderate hepatic impairment were selected as additional covariates for CL/F, and ATTR-PN as an additional covariate for F. These covariates were incorporated in the final model.

The PPK parameters (coefficient of variations, %) estimated from the final model were as follows: CL/F = 0.228 L/h (1.79%), V_c/F = 11.5 L (1.33%), V_p/F = 4.51 L (4.35%), and ka = 3.13 h^{-1} (8.41%). The Q/F was estimated from the oral formulation data (0.230 L/h).

6.2.5 Exposure-response analysis (CTD 5.3.3.5.3)

To evaluate the relationship between TTR percent stabilization and the plasma TTR/tafamidis molar ratio following the administration of tafamidis, an exposure-response analysis was performed based on plasma tafamidis concentration, TTR concentration, and TTR percent stabilization (3662 time points in 660 subjects)

3) Clinical studies (a total of 21) in healthy adults or patients with ATTR-PN

4) Candidate covariates for CL/F included sex, age, race, baseline creatinine clearance, baseline ALT, baseline AST, baseline bilirubin, and hepatic impairment (normal, mild, or moderate).
Candidate covariates for Vc/F included sex, age, race, and baseline albumin.
Candidate covariates for ka included food and formulation types.
Candidate covariates for F included food, formulation types, and subject/patient characteristics (healthy, ATTR-PN, or ATTR-CM).
The candidate covariate for absorption time lag was food.

from foreign and Japanese clinical studies in patients with ATTR-CM (Studies B3461025 and B3461028) and other clinical studies.[5)] The relationship between TTR percent stabilization and the plasma tafamidis/TTR molar ratio was described by a sigmoid E_{max} model. Characteristics of subjects (healthy subjects, patients with ATTR-PN, or patients with ATTR-CM) and TTR genotype (V30M or non-V30M in patients with ATTR-PN) were selected as covariates for E_{max} and EC_{50} influencing the pharmacodynamic (PD) parameters of tafamidis. E_{max} [95% confidence interval] and EC_{50} [95% confidence interval] in patients with ATTR-CM estimated from the final model were 236% [218%, 265%][*] and 0.897 [0.740, 1.21],[**] respectively.

6.2.6 QT evaluation study (Study B3461031, CTD 5.3.3.1.1)

To evaluate the effect of tafamidis on the QT interval, a 3-group, 3-period cross-over study (with a rest period of ≥14 days) was conducted. A single oral dose of tafamidis 400 mg, moxifloxacin 400 mg, or placebo was administered to 42 non-Japanese healthy adults.

Following a single dose of tafamidis 400 mg, t_{max} (median) was 2.02 hours, C_{max} 20.680 ± 3.7162 μg/mL, and $AUC_{0\text{-}24}$ 308.600 ± 44.392 μg·h/mL.

In terms of the difference in the mean change from baseline in the QT interval corrected by the Fridericia's correction formula (QTcF) between the tafamidis 400 mg and placebo (ΔΔQTcF), the upper limit of the 2-sided 90% confidence interval was <10 milliseconds at all time points. The lower limit of the 2-sided 90% CI for ΔΔQTcF between the moxifloxacin and placebo was >5 milliseconds at all time points up to 4 hours post-dose.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in the PK and PD of tafamidis between Japanese and non-Japanese

The applicant's explanation:

Based on the following clinical study results, there were no clear differences in the PK or PD of tafamidis between Japanese and non-Japanese subjects.

- The results of a phase I study in Japanese and non-Japanese healthy adults (Study B3461009) showed no clear differences in the plasma PK parameters of tafamidis or TTR percent stabilization following a single oral dose of tafamidis (20 or 40 mg) between Japanese and non-Japanese healthy adults (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013).
- The results of plasma tafamidis concentrations and TTR percent stabilizations following multiple oral doses of tafamidis 20 or 80 mg in Japanese patients with ATTR-CM of a global phase III study (Study B3461028) are shown in Table 8. The results in Japanese patients did not deviate substantially from the data of non-Japanese patients, although the number of Japanese patients evaluated in the study was small.

[5)] Clinical studies (a total 9) in healthy adults or patients with ATTR-PN
[*] Corrected at the time of data publication (data before correction, 207% [190%, 225%])
[**] Corrected at the time of data publication (data before correction, 0676 [0.424, 0871])

Table 8. Plasma tafamidis concentrations and TTR percent stabilization (trough) at Month 1 of treatment with multiple oral doses of tafamidis in Study B3461028

Dose (mg)	Population	Plasma tafamidis concentration (μg/mL)	TTR percent stabilization (%)
20	Non-Japanese	2.251 ± 0.931 (84)	142.3 ± 75.2 (73)
	Japanese	1.870, 3.190[a] (2)	213, 341[a] (2)
80	Non-Japanese	8.320 ± 4.011 (160)	240.8 ± 113.3 (142)
	Japanese	9.477 ± 3.231 (10)	296.0 ± 106.9 (8)

Mean ± SD (N)
a, Values from individual patients

PMDA's view:

The submitted study results and the above explanation indicate no clear differences in the PK or PD of tafamidis between Japanese and non-Japanese. PMDA has therefore concluded that the participation of Japanese patients in Study B3461028 (a global study) was appropriate from the viewpoint of the PK and PD of tafamidis.

6.R.2 Rationale for the dosage regimen selected for Study B3461028

The applicant's explanation:

In clinical studies involving patients with ATTR-PN or ATTR-CM conducted before the initiation of Study B3461028 (a phase III study), tafamidis was administered at a dose of 20 mg based on the plasma tafamidis concentrations, TTR concentrations, TTR percent stabilization, and other data from the clinical pharmacology studies (dose range investigated, 20 to 120 mg) that were available at the time of the planning of each study. Subsequently, Study B3461040 was conducted in healthy adults to assess the relationship between TTR percent stabilization and the plasma tafamidis/TTR molar ratio following a single dose of tafamidis (240 to 480 mg). The results suggested that doses of >20 mg may enhance TTR stabilization [see Section "6.2.2.1 Single dose study in non-Japanese population"]. Therefore, it was decided that the dose that would maximize TTR percent stabilization be re-examined.

Based on the results of a foreign clinical study in healthy adults (Study Fx1A9-109) and other data, the range of plasma tafamidis/TTR molar ratio in steady state during treatment with multiple oral doses of tafamidis 20 to 120 mg once daily was estimated for each dose level. The estimated molar ratios and the relationship between TTR percent stabilization and plasma tafamidis/TTR molar ratio observed in Study B3461040 suggested that the TTR percent stabilization would reach or nearly reach a plateau at ≥80 mg (Figure 2). The relationship between the TTR percent stabilization and plasma tafamidis/TTR molar ratio observed in patients with ATTR-CM treated with tafamidis 20 mg in Study B3461025 did not differ substantially from the results of Study B3461040, although the range of the plasma tafamidis/TTR molar ratio assessed in Study B3461025 was smaller. Therefore, the relationship between the TTR percent stabilization and plasma tafamidis/TTR molar ratio observed in healthy adults in Study B3461040 was able to use in estimating the dose of tafamidis for patients with ATTR-CM. On the other hand, the $AUC_{0\text{-}24}$ values observed at the no observed adverse effect level (NOAEL) in a 26-week repeated oral dose study in rats and a 39-week repeated oral dose study in dogs were from 9.1 to 20 times the AUC_{τ} value that was expected to be achieved with multiple oral doses of tafamidis 80 mg administered once daily in humans. This suggests the possibility that tafamidis administered at >80 mg may not ensure an adequate safety margin.

Based on the above study results, the maximum dose of tafamidis assessed in Study B3461028 was set at 80 mg so that the TTR percent stabilization would plateau and an adequate safety margin could be ensured.

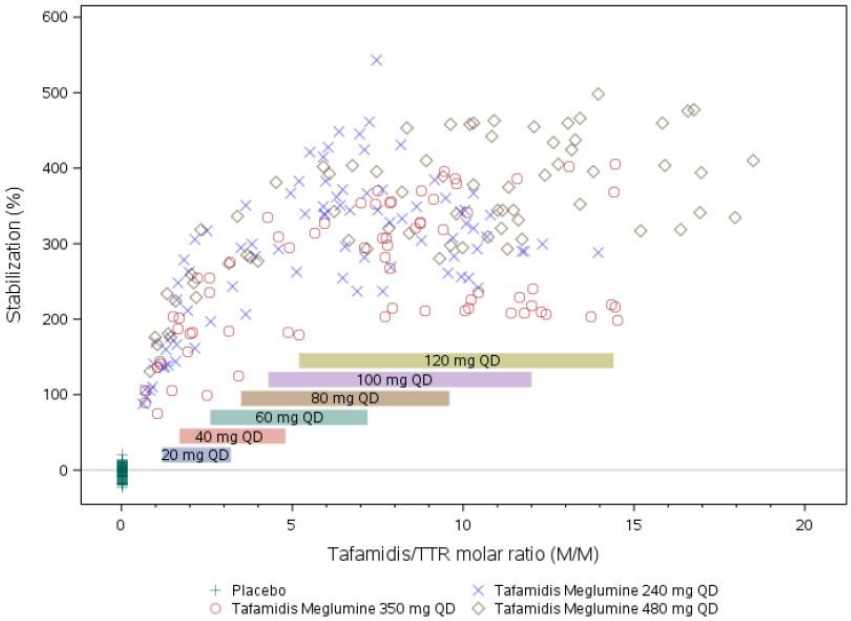

Figure 2. Relationship between TTR percent stabilization and plasma tafamidis/TTR molar ratio
The horizontal bars indicate the range of plasma tafamidis/TTR molar ratio calculated from the estimated C_{min} and C_{max} values at each dose level.

PMDA's view:

Based on the results of Study B3461040, etc., 80 mg was the appropriate maximum dose used in Study B3461028 from the viewpoint of the PK and PD of tafamidis. However, the dosage regimens of tafamidis should continue to be discussed with the efficacy and safety results of Study B3461028 taken into account [see Section "7.R.5 Dosage and administration"].

6.R.3 Effects of ATTR-CM disease type or TTR genotype on the PK and PD of tafamidis

The applicant's explanation:

Table 9 summarizes the plasma tafamidis concentrations and TTR percent stabilization observed in the tafamidis 20 mg group and the tafamidis 80 mg group of Study B3461028 by ATTR-CM disease type and TTR genotype. At these 2 dose levels, the plasma tafamidis concentration and TTR percent stabilization (trough) at Month 1 of treatment with multiple oral doses were generally similar, regardless of ATTR-CM disease type or TTR genotype.

Table 9. Plasma tafamidis concentrations and TTR percent stabilization (trough) at Month 1 of treatment with multiple oral doses of tafamidis in Study B3461028

TTR genotype	Plasma tafamidis concentration (μg/mL)		TTR percent stabilization (%)	
	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis 20 mg	Tafamidis 80 mg
Wild-type	2.157 ± 0.812 (67)	8.125 ± 3.786 (131)	143.9 ± 67.9 (63)	232.1 ± 96.2 (126)
Variants	2.612 ± 1.211 (19)	9.274 ± 4.479 (39)	156.5 ± 121.8 (12)	305.1 ± 167.9 (24)
Mutant variant				
V122I	2.473 ± 1.524 (9)	9.296 ± 4.558 (24)	161.0 ± 168.8 (5)	351.4 ± 193.2 (13)
T60A	2.218 ± 1.062 (4)	4.640, 13.000 [a] (2)	95, 53 [a] (2)	285, 281 [a] (2)
I68L	2.827 ± 0.768 (3)	11.638 ± 5.332 (6)	131.7 ± 67.5 (3)	240.5 ± 134.3 (6)
V20I		4.640 (1)		-
V30M	2.930 (1)	7.500, 5.810 [a] (2)	-	409, 231 [a] (2)
E89K		4.490 (1)		106 (1)
F33L	3.060 (1)		270 (1)	
F44Y	4.030 (1)		260 (1)	
F64L		11.400 (1)		–[b]
P24S		10.700, 6.560 [a] (2)		–

Mean ± SD (N)
-, Not determined
a, Values from individual patients
b, A phase II study in non-Japanese patients with ATTR-PN (non-V30M) (Study Fx1A-201) submitted for the initial approval demonstrated that treatment with tafamidis 20 mg achieved TTR stabilization (TTR percent stabilization [mean ± SD]; 290.1 ± 69.5% at Week 6, 214.2 ± 90.7% at Month 12; N = 4 at both time points).

PMDA's view:

The submitted study results suggested no clear differences in the PK or PD of tafamidis between the ATTR-CM disease types. However, the number of patients with each genotype was extremely small, and the available data including the results of the clinical studies conducted for the initial approval did not demonstrate the stabilization of TTR with V20I or V24S mutation via tafamidis therapy. The effects of ATTR-CM disease type and TTR genotype on the efficacy of tafamidis should continue to be evaluated [see Section "7.R.2.3 Efficacy by ATTR-CM disease type or TTR genotype"].

6.R.4 PK interactions with drugs that are substrates for BCRP

The applicant's explanation about a possible clinically relevant pharmacokinetic interactions caused by the use of tafamidis in combination with a drug that is a substrate for BCRP:

The results of *in vitro* studies suggested that tafamidis inhibits the activity of BCRP. However, no clinical studies have evaluated the effects of tafamidis on the PK of drugs that are substrates for BCRP. Table 10 shows the incidences of adverse events in patients who received ≥1 dose of a drug that is a substrate for BCRP (imatinib, rosuvastatin, or sulfasalazine) in Study B3461028. Although only a limited number of patients received any of these drugs in Study B3461028, the incidences of serious adverse events and adverse events leading to study discontinuation did not increase in a dose-dependent manner, or did not tend to be higher in the tafamidis groups than in the placebo group. Therefore, clinically relevant PK interactions are unlikely to occur when a clinically recommended dose of tafamidis is administered in combination with a drug that is a substrate for BCRP. The fact that tafamidis has been shown to inhibit the activity of BCRP in *in vitro* studies will be highlighted in the package insert, and no further cautionary advice will be necessary.

Table 10. Incidences of adverse events
(Patients who received drugs that are substrates for BCRP in the safety analysis set of Study B3461028)

Adverse events	Placebo (N = 8)	Tafamidis 20 mg (N = 5)	Tafamidis 80 mg (N = 16)
Adverse events	100 (8)	100 (5)	100 (16)
Serious adverse events	100 (8)	100 (5)	68.8 (11)
Adverse events leading to study discontinuation	37.5 (3)	40.0 (2)	25.0 (4)

% (n)

PMDA's view:

Based on the available data, the applicant's decision to use the package insert alone to communicate the possible inhibitory effect of tafamidis on BCRP is reasonable. However, the limited data of patients receiving tafamidis in combination with drugs that are substrates for BCRP do not suffice to conclude at present that such combination use is unlikely to cause clinically relevant PK interactions. Therefore, the applicant should continue to collect data on the PK interactions between tafamidis and BCRP substrates in the post-marketing setting.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from 5 clinical studies presented in Table 11 [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"].

Table 11. Summary of key clinical studies

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Foreign	B3461040	I	Non-Japanese healthy adults	9	Single oral dose of placebo, or tafamidis 240 mg, 350 mg, or 480 mg	Safety PK/PD
	Foreign	B3461056	I	Non-Japanese healthy adults	30	PK comparison between Vyndaqel (tafamidis meglumine) 80 mg and tafamidis (free acid) 61 mg	PK Safety
	Foreign	B3461031	I	Non-Japanese healthy adults	42	Single oral dose of placebo, tafamidis 400 mg, or moxifloxacin 400 mg	Safety PK
	Foreign	B3461025	II	Non-Japanese patients with wild-type or V122I ATTR-CM	35	Repeated oral doses of tafamidis 20 mg once daily for 12 months	PK/PD Efficacy Safety
	Global	B3461028	III	Japanese or non-Japanese patients with wild-type or variant ATTR-CM	441	Repeated oral doses of placebo, tafamidis 20 mg, or tafamidis 80 mg once daily for 30 months	Efficacy Safety

7.1 Phase I studies

7.1.1 Foreign phase I study (Study B3461040, CTD 5.3.3.1.2, July to September 2012)

A 3-group, 3-period dose-escalation, cross-over study (with a rest period of 14 days) was conducted at 1 site outside Japan to evaluate the safety, PK, and PD of a single oral dose of tafamidis in 9 non-Japanese healthy adults.

Subjects received a single oral dose of placebo or tafamidis 240, 350, or 480 mg.

Adverse events were reported in 3 of 8 subjects in the placebo group, 2 of 6 subjects in the tafamidis 240 mg group, 4 of 5 subjects in the tafamidis 350 mg group, and 2 of 5 subjects in the tafamidis 480 mg group. A causal relationship to the study drug could not be ruled out in 2 subjects in the placebo group (ulcer/pruritus, folliculitis), 2 subjects in the tafamidis 350 mg group (hordeolum, presyncope/photosensitivity reaction), and 1 subject in the tafamidis 480 mg group (hordeolum).

No subjects died from adverse events or no other serious adverse events were reported.

Adverse events leading to study discontinuation were reported in 1 patient (pruritus) in the placebo group and 1 patient (presyncope) in the tafamidis 350 mg group. A causal relationship to the study drug could not be ruled out for either events.

7.1.2 Foreign phase I study (Study B3461056, CTD 5.3.3.1.3, September 2017 to March 2018)

A 2-group, 2-period cross-over study (with a rest period of ≥16 days) was conducted to compare the PK of tafamidis following multiple oral doses once daily for 7 days between Vyndaqel 80 mg (containing 48.8 mg of tafamidis meglumine) and a preparation containing 61 mg tafamidis (free acid) in 30 non-Japanese healthy adults.

All 30 subjects treated with the study drug were included in the safety analysis set.

In the Vyndaqel 80 mg group, adverse events were reported in 12 of 30 subjects. A causal relationship to the study drug could not be ruled out in 9 subjects (headache in 2 subjects; fatigue, blepharospasm/headache/muscle spasms, abdominal pain/headache, gastrointestinal pain/hyperchlorhydria/fatigue/pain in extremity/diarrhoea/headache, discomfort/back pain, musculoskeletal stiffness, and acne in 1 subject each).

No subject died from adverse events.

A serious adverse event was reported in 1 subject (facial bones fracture), for which a causal relationship to the study drug was ruled out. There were no adverse events leading to study discontinuation.

7.1.3 Foreign phase I study (Study B3461031, CTD 5.3.3.1.1, January to April 2013)

A 3-group, 3-period, open-label, cross-over study (with a rest period of 14 days) was conducted at 3 sites outside Japan to evaluate the safety and PK of a single oral dose of tafamidis in 42 non-Japanese healthy adults.

Subjects received a single oral dose of placebo, tafamidis 400 mg, or moxifloxacin 400 mg.

All 42 subjects treated with the study drug were included in the safety analysis set.

Adverse events were reported in 9 of 42 subjects in the placebo group, 10 of 42 subjects in the tafamidis group, and 12 of 42 subjects in the moxifloxacin group. A causal relationship to the study drug could not be ruled out in 6 subjects (acne in 3 patients; headache, nausea/vomiting/chills/headache, and insomnia in 1 subject each) in the placebo group, 7 subjects (acne in 2 subjects; headache, headache/dry skin, fatigue/myalgia, folliculitis, and throat irritation in 1 patient each) in the tafamidis group, and 8 subjects (nausea in 2 subjects; nausea/dizziness, abdominal pain/dizziness, diarrhoea/fatigue, folliculitis, headache, and acne in 1 subject each) in the moxifloxacin group.

There were no adverse events resulting in death, other serious adverse events, or adverse events leading to study discontinuation.

7.2 Phase II study

7.2.1 Foreign phase II study (Study B3461025, CTD 5.3.4.2.1, August 2008 to January 2010)

An open-label, uncontrolled study was conducted at 6 sites outside Japan to evaluate the TTR percent stabilization, efficacy, safety, and PK of tafamidis in non-Japanese patients with wild-type or V122I mutant ATTR-CM (target sample size, ≤40).

Patients received multiple oral doses of tafamidis 20 mg once daily for 12 months.

Patients aged ≥40 were eligible to participate in the study if they (1) had participated in Study Fx-001 (a non-interventional, observational study)[6)] or (2) had documented V122I mutant or wild-type ATTR-CM with New York Heart Association (NYHA) class I or II. Wild-type ATTR-CM was defined by (1) TTR amyloid deposits in cardiac biopsy tissues or (2) the left ventricle wall >12 mm-thick on echocardiography and TTR amyloid deposits in non-cardiac biopsy tissues. V122I mutant ATTR-CM was defined by (1) amyloid in cardiac biopsy tissues or (2) the left ventricle wall >12 mm-thick on echocardiography and amyloid in non-cardiac biopsy tissues.

All 35 enrolled patients (wild-type, 31; V122I mutant, 4) were treated with the study drug and were included in the safety analysis set and the intent-to-treat (ITT) population. The primary efficacy analysis set was the ITT population. Of these 35 patients, 3 patients discontinued the study. The causes of study discontinuation were adverse events, immunoglobulin amyloidosis, and death in 1 patient each.

The proportion of patients who achieved TTR stabilization (i.e., a TTR percent stabilization ≥32%[7)]) at Week 6 (the primary endpoint) was 97.1% (34 of 35 patients). The exploratory endpoint, which was composed of all-cause mortality and the frequency of cardiovascular hospitalizations at Month 12, was 25.7% (9 of 35 patients).

[6)] A non-interventional, observational study in patients with familial cardiac amyloidosis or senile systemic amyloidosis, aged ≥18 (April 2006 to December 2008). A total of 29 patients (wild-type, 18 patients; V122I mutant, 11 patients) were enrolled. The mean follow-up period was 15.5 months.

[7)] This cut-off value was set as a cut-off value that was not achieved by any placebo-treated subject, and that was achieved by almost all subjects treated with tafamidis 20 mg in Study Fx-005 at the initial application (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013).

Specifically, the all-cause mortality was 5.7% (2 of 35 patients) and the frequency of cardiovascular hospitalizations was 25.7% (9 of 35 patients) (including patients categorized into both).

The safety analysis revealed that the incidence of adverse events was 100% (35 of 35 patients). Table 12 shows the common adverse events.

Table 12. Adverse events reported with an incidence of ≥10% (safety analysis set)

	Entire study population (N = 35)
Dyspnoea	31.4 (11)
Cardiac failure congestive	25.7 (9)
Fatigue	22.9 (8)
Dizziness	20.0 (7)
Diarrhoea	20.0 (7)
Dizziness postural	17.1 (6)
Dyspnoea exertional	17.1 (6)
Atrial fibrillation	17.1 (6)
Upper respiratory tract infection	17.1 (6)
Oedema peripheral	17.1 (6)
Weight decreased	17.1 (6)
Balance disorder	14.3 (5)
Constipation	14.3 (5)
Nausea	14.3 (5)
Weight increased	14.3 (5)
Cardiac failure	11.4 (4)
Hepatomegaly	11.4 (4)

% (n)

Two patients died from adverse events (haemorrhagic stroke and amyloidosis). A causal relationship to the study drug was ruled out for both events.

Other serious adverse events were reported in 42.9% (15 of 35) of patients, including cardiac failure congestive in 9 patients, atrial fibrillation in 3 patients, fall in 3 patients, cardiac failure in 2 patients, and syncope in 2 patients. Among the serious adverse events reported, a causal relationship to the study drug could not be ruled out for syncope, coordination abnormal, fall/ cardiac failure congestive, and fall in 1 patient each.

One patient discontinued the study due to an adverse event (glioblastoma multiforme), for which a causal relationship to the study drug was ruled out.

7.3 Phase III study

7.3.1 Global phase III study (Study B3461028, CTD 5.3.5.1.1, December 2013 to February 2018)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 54 sites in and outside Japan to evaluate the efficacy and safety of tafamidis in Japanese and non-Japanese patients with wild-type or variant ATTR-CM (target sample size, 400).

Patients received oral doses of placebo, tafamidis 20 mg, or tafamidis 80 mg once daily for 30 months.

Patients with wild-type or variant ATTR-CM between 18 and 90 years of age were eligible for the study, if they had a history of cardiac failure with ≥1 related hospitalization or ongoing cardiac failure with volume overload or elevated intracardiac pressure that had been treated with a diuretic agent. Wild-type ATTR-CM was defined by (1) no mutant TTR genotype, (2) an end-diastolic interventricular septal wall >12 mm-thick on echocardiography, (3) amyloid deposits in biopsy tissues, and (4) TTR precursor protein identified by immunohistochemical staining, myocardial scintigraphy, or mass spectrometry. Variant ATTR-CM was defined by (1) a symptom of cardiomyopathy and a cardiomyopathy-related mutant TTR genotype, (2) an end-diastolic interventricular septal wall >12 mm-thick on echocardiography, and (3) amyloid deposits in biopsy tissues.

Enrolled patients were stratified according to NYHA class (I vs II/ III) and TTR genotype (wild-type vs variant), and then randomized to the placebo, tafamidis 20 mg, or tafamidis 80 mg group at a ratio of 2:1:2. Of 441 randomized patients (wild-type, 335 including 17 Japanese; variant, 106), 177 patients (including 5 Japanese) were assigned to the placebo group, 88 (including 2 Japanese) to the tafamidis 20 mg group, and 176 (including 10 Japanese) to the tafamidis 80 mg group (the pooled tafamidis group; 264). All 441 randomized patients were treated with the study drug and were included in the safety analysis set. The 441 patients underwent ≥1 post-baseline efficacy evaluation and were included in the ITT population. The ITT population was the primary efficacy analysis set. A total of 183 patients (92 in the placebo group, 28 in the tafamidis 20 mg group, and 63 [including 3 Japanese] in the tafamidis 80 mg group) discontinued the study. The reasons for discontinuation included death in 77 patients (38 in the placebo group, 14 in the 20 mg group, and 25 [including 1 Japanese] in the tafamidis 80 mg group), consent withdrawal in 62 patients (37 in the placebo group, 8 in the tafamidis 20 mg group, and 17 in the tafamidis 80 mg group), adverse events in 28 patients (11 in the placebo group, 5 in the tafamidis 20 mg group, and 12 [including 2 Japanese] in the tafamidis 80 mg group), and "other" in 13 patients (5 in the placebo group, 1 in the tafamidis 20 mg group, and 7 in the tafamidis 80 mg group), protocol deviations in 2 patients (1 in the placebo group and 1 in the tafamidis 80 mg group), and lost to follow-up in 1 patient in the tafamidis 80 mg group.

A comparison of the primary efficacy endpoint, which was composed of all-cause mortality (including heart transplantation and implantation of a mechanical-cardiac assist device) and the frequency of cardiovascular-related hospitalizations[8)] showed a significant difference between the pooled tafamidis group and the placebo group (Table 13, P = 0.0006, Finkelstein-Schoenfeld method). Survival rates were 72.7% (64 of 88 patients) in the tafamidis 20 mg group and 69.3% (122 of 176 patients) in the tafamidis 80 mg group. The average frequency of cardiovascular-related hospitalizations in surviving patients was 0.218/year in the tafamidis 20 mg group and 0.339/year in the tafamidis 80 mg group. All deaths and all hospitalizations, including the individual components of the primary efficacy endpoint, were evaluated as the secondary endpoints (Table 14).

[8)] The Endpoint Adjudication Committee determined whether each death or hospitalization was cardiovascular-related in a blinded manner.

Table 13. All-cause mortality and frequency of cardiovascular-related hospitalizations (Primary endpoint, ITT population)

Entire study population	Placebo (N = 177)	Pooled tafamidis (N = 264)
Survival rate[a,b] (% (n))	57.1 (101)	70.5 (186)
Frequency of cardiovascular-related hospitalizations in surviving patients[a,b] (/year)	0.455	0.297
P-value[b,c] (inter-group comparison)	0.0006	

a, Summary statistics for the individual components of the primary endpoint at Month 30
b, Heart transplantation and implantation of a mechanical-cardiac assist device, leading to study discontinuation, were treated as death in the primary analysis.
c, "All-cause mortality," followed by "frequency of cardiovascular-related hospitalizations" were hierarchically assessed by the Finkelstein-Schoenfeld method (*Statist Med*. 1999;18:1341-54), which was based on pairwise comparisons between each patient and all others, and the scores assigned by these comparisons were used to test the composite primary endpoint between the placebo group and the pooled tafamidis group. To compare all-cause mortality and the frequency of cardiovascular-related hospitalizations taking into account "NYHA class" and "TTR genotype," pairwise comparisons were performed among 4 stratifications based on these 2 factors.

Table 14. All deaths and all hospitalizations (Secondary endpoints, ITT population)

Entire study population	Placebo (N = 177)	Pooled tafamidis (N = 264)	Tafamidis 20 mg (N = 88)	Tafamidis 80 mg (N = 176)
All deaths	40.7 (72)	27.3 (72)	26.1 (23)	27.8 (49)
Cardiovascular-related deaths	28.2 (50)	20.1 (53)	19.3 (17)	20.5 (36)
Unknown	5.1 (9)	1.9 (5)	1.1 (1)	2.3 (4)
Non-cardiovascular-related deaths	7.3 (13)	5.3 (14)	5.7 (5)	5.1 (9)
Heart transplantation	2.3 (4)	2.7 (7)	1.1 (1)	3.4 (6)
Implantation of a cardiac mechanical assist device	0 (0)	0.8 (2)	0 (0)	1.1 (2)
All hospitalizations	76.8 (136)	72.0 (190)	73.9 (65)	71.0 (125)
Cardiovascular-related hospitalizations	60.5 (107)	52.3 (138)	47.7 (42)	54.5 (96)
Unknown	0 (0)	1.1 (3)	1.1 (1)	1.1 (2)
Non-cardiovascular-related hospitalizations	45.2 (80)	47.3 (125)	50.0 (44)	46.0 (81)
Japanese subpopulation	Placebo (N = 5)	Pooled tafamidis (N = 12)	Tafamidis 20 mg (N = 2)	Tafamidis 80 mg (N = 10)
All deaths	0 (0)	25.0 (3)	0 (0)	30.0 (3)
Cardiovascular-related deaths	0 (0)	8.3 (1)	0 (0)	10.0 (1)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
Non-cardiovascular-related deaths	0 (0)	16.7 (2)	0 (0)	20.0 (2)
Heart transplantation	0 (0)	0 (0)	0 (0)	0 (0)
Implantation of a cardiac mechanical assist device	0 (0)	0 (0)	0 (0)	0 (0)
All hospitalizations	80.0 (4)	75.0 (9)	100 (2)	70.0 (7)
Cardiovascular-related hospitalizations	80.0 (4)	33.3 (4)	50.0 (1)	30.0 (3)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
Non-cardiovascular-related hospitalizations	0 (0)	66.7 (8)	100 (2)	60.0 (6)

% (n)

Figure 3 shows the Kaplan-Meier curves of time to death from any cause, which was a component of the primary endpoint. The hazard ratio [95% confidence interval] for the pooled tafamidis group versus the placebo group was 0.698 [0.508, 0.958] (Cox proportional hazards model).

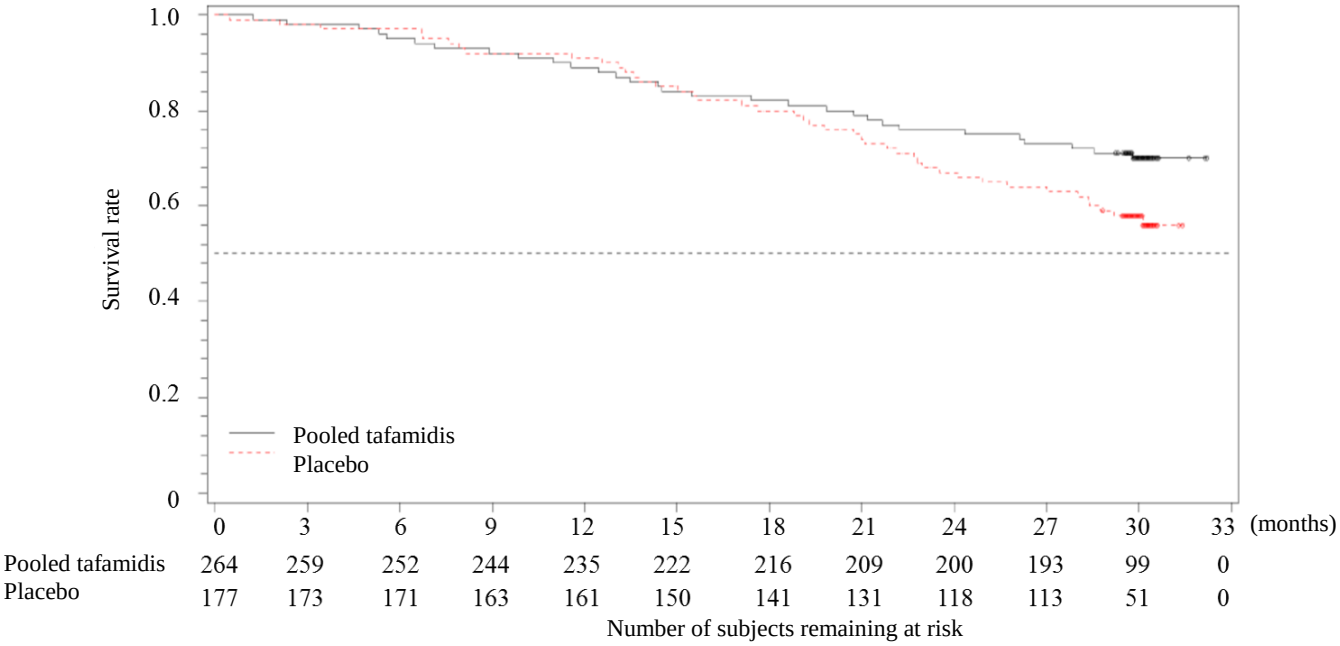

Figure 3. Time to all-cause death[a]
(Kaplan-Meier curves: secondary endpoint, entire study population, ITT population)
a, Heart transplantation and implantation of a mechanical-cardiac assist device, leading to study discontinuation were treated as death.

Table 15 shows the results of other key secondary endpoints.

Table 15. Distance walked during 6-minute walk test and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) scores (secondary endpoints, ITT population)

Entire study population		Placebo	Pooled tafamidis	Tafamidis 20 mg	Tafamidis 80 mg
Distance walked during 6-minute walk test (m)	Baseline	N = 177 353.3 ± 126.0	N = 264 350.6 ± 121.3	N = 88 362.1 ± 123.2	N = 176 344.8 ± 120.3
	Month 30	N = 70 333.8 ± 117.5	N = 155 370.4 ± 119.4	N = 54 381.1 ± 106.0	N = 101 364.7 ± 126.1
	Change from baseline	N = 70 −89.7 ± 105.2	N = 155 −30.5 ± 87.9	N = 54 −29.2 ± 93.3	N = 101 −31.2 ± 85.3
KCCQ-OS score	Baseline	N = 177 65.9 ± 21.7	N = 264 67.3 ± 21.4	N = 88 67.6 ± 21.6	N = 176 67.1 ± 21.3
	Month 30	N = 84 53.8 ± 24.4	N = 170 68.2 ± 21.9	N = 60 67.3 ± 23.0	N = 110 68.8 ± 21.4
	Change from baseline	N = 84 −14.6 ± 21.4	N = 170 −3.9 ± 19.3	N = 60 −3.8 ± 19.5	N = 110 −3.9 ± 19.3
Japanese subpopulation		Placebo	Pooled tafamidis	Tafamidis 20 mg	Tafamidis 80 mg
Distance walked during 6-minute walk test (m)	Baseline	N = 5 388.2 ± 111.4	N = 12 338.9 ± 100.0	N = 2 320.0, 476.0 [a]	N = 10 327.1 ± 99.7
	Month 30	N = 2 300.0, 353.0 [a]	N = 8 322.8 ± 110.5	N = 2 374.0, 389.0 [a]	N = 6 303.2 ± 123.4
	Change from baseline	N = 2 −184.0, 20.0 [a]	N = 8 −25.9 ± 46.9	N = 2 −87.0, 54.0 [a]	N = 6 −29.0 ± 32.3
KCCQ-OS score	Baseline	N = 5 71.8 ± 17.7	N = 12 78.0 ± 17.2	N = 2 56.5, 85.4 [a]	N = 10 79.4 ± 17.4
	Month 30	N = 5 46.7 ± 31.0	9 63.4 ± 23.1	N = 2 59.6, 72.9 [a]	N = 7 62.6 ± 26.3
	Change from baseline	N = 5 −25.0 ± 24.3	9 −9.8 ± 24.3	N = 2 −12.5, 3.1 [a]	N = 7 −11.3 ± 27.5

Mean ± SD
a, Values from individual patients

In the entire study population, the incidences of adverse events were 98.9% (175 of 177 patients) in the placebo group, 98.9% (87 of 88 patients) in the tafamidis 20 mg group, and 98.3% (173 of 176 patients) in the tafamidis 80 mg group. Table 16 shows the common adverse events in the entire study population. In the Japanese subpopulation, the incidences of adverse events were 100% (5 of 5 patients) in the placebo group, 100% (2 of 2 patients) in the tafamidis 20 mg group, and 80.0% (8 of 10 patients) in the tafamidis 80 mg group (Table 17).

Table 16. Adverse events reported with an incidence of ≥10% in any treatment group (Entire study population, safety analysis set)

	Placebo (N = 177)	Tafamidis 20 mg (N = 88)	Tafamidis 80 mg (N = 176)
Atrial fibrillation	18.6 (33)	18.2 (16)	19.9 (35)
Cardiac failure	33.9 (60)	34.1 (30)	26.1 (46)
Cardiac failure acute	9.6 (17)	4.5 (4)	13.6 (24)
Cardiac failure congestive	18.6 (33)	19.3 (17)	12.5 (22)
Constipation	16.9 (30)	15.9 (14)	14.8 (26)
Diarrhoea	22.0 (39)	11.4 (10)	12.5 (22)
Nausea	20.3 (36)	10.2 (9)	11.4 (20)
Asthenia	6.2 (11)	12.5 (11)	10.2 (18)
Fatigue	18.6 (33)	18.2 (16)	16.5 (29)
Oedema	11.3 (20)	8.0 (7)	6.3 (11)
Oedema peripheral	17.5 (31)	19.3 (17)	17.0 (30)
Bronchitis	10.7 (19)	10.2 (9)	11.9 (21)
Pneumonia	9.6 (17)	11.4 (10)	13.6 (24)
Urinary tract infection	15.3 (27)	10.2 (9)	9.1 (16)
Fall	23.7 (42)	30.7 (27)	24.4 (43)
Weight decreased	10.2 (18)	6.8 (6)	4.5 (8)
Decreased appetite	14.1 (25)	9.1 (8)	8.0 (14)
Fluid overload	16.4 (29)	14.8 (13)	10.8 (19)
Gout	16.4 (29)	11.4 (10)	10.2 (18)
Hypokalaemia	10.7 (19)	9.1 (8)	9.1 (16)
Arthralgia	11.9 (21)	9.1 (8)	11.4 (20)
Back pain	13.6 (24)	10.2 (9)	9.7 (17)
Muscle spasms	7.9 (14)	11.4 (10)	8.5 (15)
Pain in extremity	11.9 (21)	6.8 (6)	15.3 (27)
Dizziness	20.9 (37)	19.3 (17)	14.2 (25)
Insomnia	12.4 (22)	13.6 (12)	11.9 (21)
Acute kidney injury	16.4 (29)	13.6 (12)	9.7 (17)
Haematuria	9.6 (17)	11.4 (10)	5.7 (10)
Cough	16.9 (30)	18.2 (16)	11.9 (21)
Dyspnoea	31.1 (55)	23.9 (21)	17.0 (30)
Pleural effusion	18.1 (32)	13.6 (12)	8.0 (14)
Hypotension	10.7 (19)	13.6 (12)	10.8 (19)

% (n)

Table 17. Adverse events reported in ≥2 patients in any treatment group (Japanese subpopulation, safety analysis set)

	Placebo (N = 5)	Tafamidis 20 mg (N = 2)	Tafamidis 80 mg (N = 10)
Anaemia	40.0 (2)	50.0 (1)	0 (0)
Arrhythmia	0 (0)	0 (0)	20.0 (2)
Atrial flutter	40.0 (2)	0 (0)	0 (0)
Cardiac failure	60.0 (3)	50.0 (1)	10.0 (1)
Hypothyroidism	80.0 (4)	0 (0)	0 (0)
Constipation	20.0 (1)	0 (0)	20.0 (2)
Cystitis	0 (0)	0 (0)	30.0 (3)
Gastroenteritis	0 (0)	0 (0)	20.0 (2)
Nasopharyngitis	40.0 (2)	50.0 (1)	20.0 (2)
Contusion	0 (0)	50.0 (1)	20.0 (2)
Skin abrasion	0 (0)	0 (0)	20.0 (2)
Hyperkalaemia	40.0 (2)	0 (0)	20.0 (2)
Arthralgia	0 (0)	0 (0)	20.0 (2)
Back pain	40.0 (2)	0 (0)	0 (0)
Carpal tunnel syndrome	20.0 (1)	0 (0)	20.0 (2)
Insomnia	40.0 (2)	0 (0)	30.0 (3)
Benign prostatic hyperplasia	20.0 (1)	0 (0)	20.0 (2)
Oropharyngeal pain	0 (0)	0 (0)	20.0 (2)
Sputum retention	40.0 (2)	0 (0)	0 (0)
Pruritus	20.0 (1)	0 (0)	20.0 (2)
Hypotension	20.0 (1)	0 (0)	20.0 (2)

% (n)

Adverse events resulting in death occurred in 40.7% (72 of 177) of patients in the placebo group, 26.1% (23 of 88) of patients in the tafamidis 20 mg group, and 27.8% (49 of 176) of patients in the tafamidis 80 mg group. A causal relationship to the study drug was ruled out for all of these events. In the Japanese subpopulation, no patients in the placebo or the tafamidis 20 mg group died from adverse events, but 30.0% (3 of 10) of patients in the tafamidis 80 mg group died from adverse events.

Serious adverse events occurred in 79.1% (140 of 177) of patients in the placebo group, 75.0% (66 of 88) of patients in the tafamidis 20 mg group, and 75.6% (133 of 176) of patients in the tafamidis 80 mg group. A causal relationship to the study drug could not be ruled out in 2.3% (4 of 177) of patients in the placebo group (ventricular fibrillation, cardiac failure congestive/disease progression, gallbladder adenocarcinoma, and dizziness/lethargy/dyspnoea in 1 patient each), 2.3% (2 of 88) of patients in the tafamidis 20 mg group (gastritis and acute kidney injury in 1 patient each), and 1.7% (3 of 176) of patients in the tafamidis 80 mg group (pancreatitis, urinary tract infection, and liver function test increased in 1 patient each). In the Japanese subpopulation, serious adverse events occurred in 80.0% (4 of 5) of patients in the placebo group, 100% (2 of 2) of patients in the tafamidis 20 mg group, and 70.0% (7 of 10) of patients in the tafamidis 80 mg group. A causal relationship to the study drug was ruled out for all events.

Adverse events led to study discontinuation in 6.2% (11 of 177) of patients in the placebo group, 5.7% (5 of 88) of patients in the tafamidis 20 mg group, and 6.8% (12 of 176) of patients in the tafamidis 80 mg group. A causal relationship to the study drug could not be ruled out in 3 patients in the placebo group (ventricular fibrillation, gallbladder adenocarcinoma, and dizziness/lethargy/dyspnoea in 1 patient each) and 1 patient in the tafamidis 80 mg group (blood creatinine increased). In the Japanese subpopulation, no patients discontinued the study due to adverse events in the placebo group or the tafamidis 20 mg group, but 30.0% (3 of 10) of patients in the tafamidis 80 mg group discontinued the study due to adverse events, for which a causal relationship to the study drug was ruled out.

7.R Outline of the review conducted by PMDA

7.R. 1 Clinical positioning of tafamidis

The applicant's explanation:

ATTR-CM is an ultimately fatal disease characterized by the deposition of TTR amyloid in the myocardium and associated cardiac diastolic dysfunction causing restrictive cardiomyopathy and cardiac failure. Outside Japan, liver and heart transplantations are the only recognized radical therapy for ATTR-CM. However, many patients are ineligible for transplantation due to age or complications. In Japan, the Clinical Practice Guidelines for Amyloidosis do not recommend liver transplantation for variant ATTR-CM, and the Statement for Heart Transplantation (The Japanese Circulation Society, 2016) states that heart transplantation is not indicated for amyloidosis. Both in Japan and overseas, there is no approved therapeutic agent for patients with ATTR-CM. The Japanese Clinical Practice Guidelines for Amyloidosis recommend symptomatic treatments, such as diuretic therapy and implantation of a pacemaker for bradyarrhythmia (Category B Recommendation for both), and their effects are limited. Tafamidis binds to TTR, thereby stabilizing both wild-type and variant TTR tetramers in plasma (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013). The results of

Study B3461028 involving patients who had cardiac failure and documented wild-type or variant ATTR-CM demonstrated the clinically relevant efficacy and acceptable safety of tafamidis in patients with ATTR-CM [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. These results indicate that tafamidis is expected to be a novel treatment option for patients with wild-type or variant ATTR-CM, for which there are no effective therapeutic agents at present.

PMDA's view:
Based on the results of Study B3461028, tafamidis is expected to have efficacy in the treatment of patients with wild-type or variant ATTR-CM with acceptable safety [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. In Japan, no radical therapy has been established for ATTR-CM, and the recommended symptomatic therapies are not sufficiently effective. Tafamidis is a new treatment option for ATTR-CM that is a non-symptomatic therapy, and the introduction of tafamidis to clinical practice is thus meaningful.

7.R.2 Efficacy

7.R.2.1 Efficacy evaluation results

The applicant's explanation:
ATTR-CM is a rare disease, and there are only a small number of eligible patients for clinical studies. Study B3461028 was designed to verify the efficacy of tafamidis and obtain data on dose-response relationship by evaluating efficacy in the pooled tafamidis group versus the placebo group. Further, patients were assigned to the tafamidis 20 mg or tafamidis 80 mg group at the ratio of 1 to 2 so as to obtain more data on long-term treatment with tafamidis 80 mg, which had not previously been investigated. The results of Study B3461028 demonstrated a significant difference in the primary endpoint composed of all-cause mortality and the frequency of cardiovascular hospitalizations between the placebo group and the pooled tafamidis group. Declines from baseline in the distance walked during 6-minute walk test and KCCQ-OS score at Month 30 (key secondary endpoints) were smaller in the pooled tafamidis group than in the placebo group (Table 15). Thus, consistent results were obtained across the various efficacy endpoints of Study B3461028, indicating the efficacy of tafamidis in the treatment of ATTR-CM.

PMDA asked the applicant to explain the appropriateness of the use of composite endpoint, which was composed of all-cause mortality and the frequency of cardiovascular-related hospitalizations, as the primary efficacy endpoint of Study B3461028.

The applicant's explanation:
The true purpose of ATTR-CM treatment is the improvement of prognosis. However, ATTR-CM is a rare disease, and a clinical study with a sufficient sample size to verify the efficacy of tafamidis would not be feasible with the primary endpoint of all-cause mortality alone. Therefore, cardiovascular-related hospitalizations, for being clinically relevant, was combined with all-cause mortality as the primary efficacy endpoint of Study B3461028. The Finkelstein-Schoenfeld method used in the primary analysis assigned a higher importance to all-cause mortality than to cardiovascular-related hospitalizations, allowing the clinical

relevance of the 2 endpoints to be taken into account in the evaluation. Hence, the use of composite endpoint was appropriate for the efficacy evaluation of tafamidis.

PMDA's view:

Because of the following concerns, the design of Study B3461028 is not generally acceptable. It could have made the interpretation of study data extremely difficult.

- Despite insufficient information on effective doses of tafamidis, pooled data on the 2 doses of tafamidis were compared with placebo data in the primary analysis of Study B3461028. This approach raises the possibility that the efficacy of tafamidis may not be considered to have been appropriately verified at the clinically recommended dose, or it may even make it difficult to determine the clinically recommended dose.
- There is a great gap in clinical significance between all-cause mortality and the frequency of cardiovascular-related hospitalizations. In addition, the frequency of cardiovascular-related hospitalizations reflects the physician's subjective view on the necessity of hospitalization, and therefore the significance of each relevant event could differ.

However, in the situation where there was no alternative but to choose the above-mentioned study design due to feasibility constraints owing to the rarity of patients with ATTR-CM, etc., conducting the study with the not the best design would be inevitable. Therefore, at PMDA, (1) the primary efficacy of tafamidis was evaluated based on the results from the pooled tafamidis group, along with further detailed evaluation of a dose-efficacy relationship based on the results from each dose group. (2) In addition to the primary endpoint, efficacy results were further evaluated based on "all deaths" (a secondary endpoint), which was a clinically important outcome. In fact, however, a post-hoc assessment of the results from Study B3461028 showed no substantial differences in the efficacy of tafamidis between the 2 doses [see Section "7.R.5 Dosage and Administration"]. Consequently, the pooled tafamidis group-based assessment could be accepted as the primary efficacy evaluation.

There was a significant difference between the placebo and pooled tafamidis groups in the composite primary endpoint of Study B3461028, i.e., all-cause mortality and the frequency of cardiovascular-related hospitalizations (Table 13). In addition, all-cause mortality was lower in the pooled tafamidis group than in the placebo group, suggesting that tafamidis therapy improved the survival rate of patients with ATTR-CM (Table 13). In Study B3461028, heart transplantation and mechanical cardiac assist device implantation leading to study discontinuation were counted as death for evaluation of the primary endpoint. In addition, even when heart transplantation and mechanical cardiac assist device implantation leading to study discontinuation were not counted as death, the all-cause mortality in the pooled tafamidis group was lower than that in the placebo group (Table 14). Furthermore, cardiovascular-related mortality was lower in the pooled tafamidis group than in the placebo group (Table 14). Accordingly, tafamidis therapy was consistently superior to placebo in the primary endpoint and other clinically important outcomes related to death. PMDA has therefore concluded that the efficacy of tafamidis in the treatment of ATTR-CM was demonstrated. The efficacy of tafamidis by NYHA class, ATTR-CM disease type, or TTR genotype will be discussed in the subsequent sections.

7.R.2.2 Efficacy by severity of cardiac failure

The applicant's explanation about the efficacy of tafamidis according to the severity of cardiac failure:

Tables 18 and 19 show the results of the individual components of the primary endpoint and of key secondary endpoints by baseline NYHA class in Study B3461028. In the subgroup of patients with baseline NYHA class I or II, both all-cause mortality and the frequency of cardiovascular-hospitalizations were lower in the pooled tafamidis group than in the placebo group, and the results of the key secondary endpoints were favorable in the pooled tafamidis group as compared with the placebo group. In the subgroup of patients with baseline NYHA class III, all-cause mortality was lower, but the frequency of cardiovascular-related hospitalizations was higher in the pooled tafamidis group than in the placebo group. The results obtained for the key secondary endpoints were favorable in the pooled tafamidis group as compared with the placebo group. The higher frequency of cardiovascular-related hospitalizations observed in the pooled tafamidis group relative to the placebo group within the subgroup of patients with NYHA class III (more severe than NYHA I or II) may be attributable to the improved survival rate achieved by tafamidis, which prolonged survival in more severe illness, resulting in increased frequency of hospitalizations. All-cause mortality was lower in the pooled tafamidis group than in the placebo group in both NYHA subgroups, indicating that tafamidis is expected to have efficacy in patients with ATTR-CM with NYHA class III. Patients with NYHA class IV were excluded from Study B3461028.

Table 18. All-cause mortality and frequency of cardiovascular-related hospitalizations in Study B3461028
(Individual components of the primary endpoint, ITT population, subgroup analysis by NYHA class)

	NYHA class I or II		NYHA class III	
	Placebo (N = 114)	Pooled tafamidis (N = 186)	Placebo (N = 63)	Pooled tafamidis (N = 78)
Survival rate[a] (% (n))	67.5 (77)	81.2 (151)	38.1 (24)	44.9 (35)
Frequency of cardiovascular-related hospitalizations in surviving patients (/year)	0.457	0.246	0.447	0.516

a, Heart transplantation and implantation of a mechanical-cardiac assist device leading to study discontinuation were counted as death.

Table 19. All deaths and all hospitalizations, and distance walked during 6-minute walk test and KCCQ-OS scores in Study B3461028
(Secondary endpoints, ITT population, subgroup analysis by NYHA class)

	NYHA class I or II		NYHA class III	
	Placebo (N = 114)	Pooled tafamidis (N = 186)	Placebo (N = 63)	Pooled tafamidis (N = 78)
All deaths[a]	28.9 (33)	16.1 (30)	61.9 (39)	53.8 (42)
Cardiovascular-related deaths[a]	17.5 (20)	8.6 (16)	47.6 (30)	47.4 (37)
Unknown[a]	7.0 (8)	1.6 (3)	1.6 (1)	2.6 (2)
Cardiovascular-unrelated deaths[a]	4.4 (5)	5.9 (11)	12.7 (8)	3.8 (3)
Heart transplantation[a]	3.5 (4)	2.7 (5)	0 (0)	2.6 (2)
Implantation of a cardiac mechanical assist device[a]	0 (0)	0.5 (1)	0 (0)	1.3 (1)
All hospitalizations[a]	75.4 (86)	67.2 (125)	79.4 (50)	83.3 (65)
Cardiovascular-related hospitalizations[a]	61.4 (70)	41.9 (78)	58.7 (37)	76.9 (60)
Unknown[a]	0 (0)	0 (0)	0 (0)	3.8 (3)
Cardiovascular-unrelated hospitalizations[a]	43.0 (49)	47.8 (89)	49.2 (31)	46.2 (36)
Change from baseline in distance walked during 6-minute walk test at Month 30 (m)[b]	N = 57 −93.5 ± 110.0	N = 132 −27.1 ± 86.3	N = 13 −72.9 ± 82.1	N = 23 −50.0 ± 96.1
Change from baseline in KCCQ-OS score at Month 30[b]	N = 64 −15.1 ± 22.4	N = 141 −4.3 ± 18.0	N = 20 −13.3 ± 18.2	N = 29 −1.7 ± 24.8

a, % (n)
b, Mean ± SD

PMDA's view:

Because tafamidis inhibits the formation of new TTR amyloid fibrils by its action mechanism, the investigation on the effects of baseline severity of cardiac failure on the efficacy of tafamidis is important. Although the results of subgroup analyses in Tables 18 and 19 allow limited interpretation, all-cause mortality and the frequency of cardiovascular-related hospitalizations, the individual components of the primary endpoint, were lower in the pooled tafamidis group than in the placebo group within the subgroup of patients with NYHA class I or II, suggesting the efficacy of tafamidis in that subgroup. In the subgroup of patients with NYHA class III, on the other hand, the frequency of cardiovascular-related hospitalizations in the pooled tafamidis group was higher than that in the placebo group. Because of this noteworthy result and tafamidis's action mechanism, the possibility cannot be denied that tafamidis may be less effective in patients with NYHA class III than in those with NYHA class I or II. Nonetheless, tafamidis is expected to have a certain level of efficacy in patients with NYHA class ≥III as well, for the following reasons.

- All-cause mortality (the true endpoint for the treatment of ATTR-CM) was lower in the pooled tafamidis group than in the placebo group.
- As the applicant explains, patients may have lived longer in severe illness as a result of improved survival, requiring more frequent hospitalizations.
- The results of other secondary endpoints supported the efficacy of tafamidis in the subgroup of patients with NYHA class III.

The appropriateness of the above discussion will be finalized, after also taking into account the comments from the Expert Discussion.

7.R.2.3 Efficacy by ATTR-CM disease type or TTR genotype

PMDA asked the applicant to compare the pathology, clinical manifestations, prognosis, and other aspects of the disease between wild-type ATTR-CM and variant ATTR-CM, and explain whether tafamidis has promising efficacy, regardless of disease type, based on the clinical study results.

The applicant's explanation:

Clinical manifestations of variant ATTR-CM may vary by mutant genotype. However, variant ATTR-CM generally develops at an early age, presents with severe conditions, and progresses rapidly as compared with wild-type ATTR-CM (*Am Heart J.* 2012;164:222-8). ATTR-CM induced by V122I mutation, the most common variant ATTR-CM, has clinical manifestations similar to those of wild-type ATTR-CM (*Rev Esp Cardiol.* 2017;70:991-1004). Tables 20 and 21 show the results of the individual components of the primary endpoint and other key secondary endpoints in Study B3461028. Within the subgroup of patients with variant ATTR-CM, the frequency of cardiovascular-related hospitalizations was higher in the pooled tafamidis group than in the placebo group. In Study B3461028, more patients with variant ATTR-CM had baseline NYHA class III symptoms than did patients with wild-type ATTR-CM, indicating that the difference in the severity of cardiac failure was likely to be associated with more frequent hospitalizations in the pooled tafamidis group than in the placebo group within the subgroup of patients with variant ATTR-CM [see Section "7.R.2.2 Efficacy by severity of cardiac failure"]. The results for secondary endpoints other than all-cause mortality and

the frequency of cardiovascular-related hospitalizations supported the efficacy of tafamidis in both disease type subgroups. Based on the above results, tafamidis is expected to be effective both in patients with wild-type ATTR-CM and in those with variant ATTR-CM.

Table 20. All-cause mortality and frequency of cardiovascular-related hospitalizations in Study B3461028
(Individual components of the primary endpoint, ITT population, subgroup analysis by disease type)

	Variants		Wild-type	
	Placebo (N = 43)	Pooled tafamidis (N = 63)	Placebo (N = 134)	Pooled tafamidis (N = 201)
Survival rate[a] (% (n))	37.2 (16)	54.0 (34)	63.4 (85)	75.6 (152)
Frequency of cardiovascular-related hospitalizations in surviving patients (/year)	0.284	0.351	0.487	0.285

a, Heart transplantation and implantation of a mechanical-cardiac assist device leading to study discontinuation were treated as death.

Table 21. All deaths and all hospitalizations, and distance walked during 6-minute walk test and KCCQ-OS scores in Study B3461028
(Secondary endpoints, ITT population, subgroup analysis by disease type)

	Variants		Wild-type	
	Placebo (N = 43)	Pooled tafamidis (N = 63)	Placebo (N = 134)	Pooled tafamidis (N = 201)
All deaths[a]	60.5 (26)	41.3 (26)	34.3 (46)	22.9 (46)
Cardiovascular-related deaths[a]	41.9 (18)	33.3 (21)	23.9 (32)	15.9 (32)
Unknown[a]	7.0 (3)	3.2 (2)	4.5 (6)	1.5 (3)
Cardiovascular-unrelated deaths[a]	11.6 (5)	4.8 (3)	6.0 (8)	5.5 (11)
Heart transplantation[a]	2.3 (1)	6.3 (4)	2.2 (3)	1.5 (3)
Implantation of a cardiac mechanical assist device[a]	0 (0)	3.2 (2)	0 (0)	0 (0)
All hospitalizations[a]	76.7 (33)	82.5 (52)	76.9 (103)	68.7 (138)
Cardiovascular-related hospitalizations[a]	60.5 (26)	66.7 (42)	60.4 (81)	47.8 (96)
Unknown[a]	0 (0)	3.2 (2)	0 (0)	0.5 (1)
Cardiovascular-unrelated hospitalizations[a]	44.2 (19)	47.6 (30)	45.5 (61)	47.3 (95)
Change from baseline in distance walked during 6-minute walk test at Month 30 (m)[b]	N = 8 −93.9 ± 93.7	N = 24 −63.8 ± 71.3	N = 62 −89.1 ± 107.2	N = 131 −24.4 ± 89.5
Change from baseline in KCCQ-OS score at Month 30[b]	N = 10 −21.0 ± 26.4	30 −3.10 ± 23.6	N = 74 −13.8 ± 20.7	N = 140 −4.0 ± 18.4

a, % (n)
b, Mean ± SD

PMDA asked the applicant to explain whether the efficacy of tafamidis can be expected in patients with variant ATTR-CM regardless of mutant TTR genotype.

The applicant's explanation:

A total of 14 TTR genotypes were identified in patients enrolled in Study B3461028. Patients with 10 of the 14 TTR genotypes were assigned to either of the tafamidis groups. Of these 10 genotypes, 8 have been demonstrated to be stabilized by tafamidis in the clinical studies performed for the initial approval and other studies [see Section "6.R.3 Effects of ATTR-CM disease type or TTR genotype on the PK and PD of tafamidis"]. The effects of tafamidis for the remaining 2 genotypes (P24S and V20I) were not investigated in the clinical studies performed for the initial approval, and 3 patients with these genotypes were enrolled and treated with tafamidis in Study B3461028. At baseline, the plasma TTR tetramer concentration after incubation under denaturing conditions was below the quantitation limit, precluding the determination of TTR percent

stabilization at any time point in these 3 patients. However, after the start of tafamidis therapy, the plasma TTR tetramer concentration became quantifiable after incubation as well in all 3 patients (Table 22). Their FOIs were comparable with those of other patients, suggesting that tafamidis therapy stabilized TTR tetramers. These 3 patients were treated with tafamidis 80 mg and confirmed to have survived up to Month 30. Based on these results, tafamidis is expected to have a certain level of efficacy.

Table 22. Plasma TTR tetramer concentrations and FOIs at each time point in Study B3461028

Genotype	Time point	Average plasma TTR4 tetramer concentration (mg/dL)		FOI
		Before incubation	After incubation	
V20I	Baseline	9.1	<2.4	Not determined
	Month 1	16.9	5.2	0.31
	Month 6	15.6	6.1	0.39
	Month 12	14.1	4.4	0.31
	Month 18	17.2	5.0	0.29
P24S	Baseline	14.6	<2.4	Not determined
	Month 1	29.9	30.8	1.03
	Month 6	28.8	27.2	0.95
	Month 12	28.6	31.1	1.09
	Month 18	26.8	24.4	0.91
	Month 24	27.9	24.5	0.88
P24S	Baseline	11.3	<2.4	Not determined
	Month 1	25.0	12.4	0.50
	Month 6	24.8	10.4	0.42
	Month 12	24.3	13.2	0.54
	Month 18	28.8	22.1	0.77
	Month 24	27.3	16.4	0.60

PMDA's view:

All-cause mortality and cardiovascular-related mortality in the placebo group of Study B3461028 indicate a tendency toward poorer outcome in patients with variant ATTR-CM than in those with wild-type ATTR-CM. Published reports in and outside Japan do not suggest similarity between wild-type ATTR-CM and variant ATTR-CM in its pathology and outcome. However, tafamidis has been shown to stabilize both wild-type and variant TTR tetramers (see "Review Report for Vyndaqel Capsules 20 mg" dated August 8, 2013). In Study B3461028, all-cause mortality (the true endpoint for the treatment of ATTR-CM) was lower in the pooled tafamidis group than in the placebo group in both patients with wild-type and variant ATTR-CM. The results of other cardiac failure-related or other secondary endpoints were also favorable in the pooled tafamidis group as compared with the placebo group. Based on these results, tafamidis is expected to be effective against ATTR-CM of any disease type.

The 2 genotypes, P24S and V20I, were identified in 3 patients with variant ATTR-CM. In Study B3461028, because of the failure to obtain baseline values from the 3 patients, no TTR percent stabilization was determined at any time point during the 30-month study period, precluding direct assessment of TTR stabilization. These genotypes were thus to be further investigated as mentioned in Section "6.R.3 Effects of ATTR-CM disease type or TTR genotype on the PK and PD of tafamidis." However, plasma TTR tetramer concentration was quantifiable after the start of treatment with tafamidis in all 3 patients, suggesting that tafamidis stabilized TTR tetramers. The 3 patients survived throughout the study period. In addition, the 2 patients with TTR genotype P24S required no hospitalizations for cardiovascular events. Therefore, tafamidis may be administered to

patients with ATTR-CM of any TTR genotype, because no genotypes have clearly shown no promising efficacy of tafamidis in clinical studies. However, as the TTR genotypes and the number of patients assessed in the clinical studies were limited, relevant data should be collected in the post-marketing setting properly. The appropriateness of the above discussion will be finalized, taking into account the comments from the Expert Discussion.

7.R.2.4 Efficacy in the Japanese subpopulation of Study B3461028

The applicant's explanation about the appropriateness of Japanese patients' participation in Study B3461028 and the efficacy of tafamidis in the Japanese subpopulation:

ATTR-CM is diagnosed based on clinical symptoms, examinations (e.g., hematological test, echocardiography, myocardial scintigraphy, cardiac magnetic resonance imaging [MRI]), histologic identification of TTR-derived amyloid deposits by Congo Red staining and immunohistochemical staining in biopsy tissues (e.g., myocardium, gastric mucosa, rectal mucosa, abdominal wall fat), and confirmation of a TTR gene mutation (Clinical Practice Guidelines for Amyloidosis). The diagnostic criteria in Japan are similar to those used outside Japan. In particular, ATTR-CM treatment in clinical practice focuses on symptomatic therapies for cardiac failure symptoms (e.g., diuretics, pacemaker implantation) both in and outside Japan, although the indications for liver transplantation and heart transplantation differ [see Section "7.R.1 Clinical positioning of tafamidis"]. Variant ATTR-CM develops at an earlier age, becomes severer, and progresses more rapidly as compared with wild-type ATTR-CM. However, the deposition of TTR amyloid in the myocardium, which causes cardiac diastolic dysfunction resulting in restrictive cardiomyopathy and congestive cardiac failure, is common to both types of ATTR-CM. There are no known pathological differences between Japanese and non-Japanese patients. In addition, no clear differences have been identified in the PK or PD of tafamidis between Japanese patients and non-Japanese patients [see Section "6.R.1 Differences in the PK and PD of tafamidis between Japanese and non-Japanese"]. Thus, there were no clear intrinsic or extrinsic ethnic factor-related differences that may have affected the efficacy evaluation for tafamidis between the Japanese subpopulation and the entire study population of Study B3461028. Therefore, the participation of Japanese patients in Study B3461028 was appropriate.

Of the 441 patients enrolled in Study B3461028, only 17 patients were Japanese. All-cause death occurred in 3 Japanese patients in the tafamidis 80 mg group, including cardiovascular-related death in 1 patient and cardiovascular-unrelated deaths in 2 patients (pneumonia and malnutrition/pneumonia in 1 patient each). A causal relationship to the study drug was ruled out by the investigators (or sub-investigators) for all of the adverse events that resulted in deaths in these 3 patients. The frequency of cardiovascular-related hospitalizations in the Japanese subpopulation was lower in the pooled tafamidis group than in the placebo group (Table 14). The distance walked during 6-minute walk test and KCCQ-OS scores in the Japanese subpopulation were favorable in the pooled tafamidis group as compared with the placebo group (Table 15).

As above, there were no substantial differences in the results of the primary endpoint and secondary endpoints between the Japanese subpopulation and the entire study population in Study B3461028.

All Japanese patients enrolled in Study B3461028 had wild-type ATTR-CM. Height, body weight, and body mass index (BMI) tended to be lower in the Japanese subpopulation than in the entire study population. However, there were no substantial differences in other patient characteristics between the Japanese subpopulation and the entire study population. Subgroup analyses based on the patient characteristics that differed between the Japanese subpopulation and the entire study population (wild-type vs variant; > vs ≤ median body weight; > vs ≤ median BMI) showed no substantial differences in the efficacy of tafamidis between the subgroups by each patient characteristic. Although no data are available from Japanese patients treated with tafamidis for variant ATTR-CM, the efficacy of tafamidis estimated from the entire study population of Study B3461028 is expected in Japanese patients as well, considering that the PK and PD of tafamidis did not differ substantially between the disease types (wild-type vs variant) or ethnic groups (Japanese vs non-Japanese) [see Sections "6.R.3 Effects of ATTR-CM disease type or TTR genotype on the PK and PD of tafamidis" and "6.R.1 Differences in the PK and PD of tafamidis between Japanese and non-Japanese"].

PMDA's view:

Based on the applicant's explanation, there were no differences seen between Japanese and non-Japanese patients in intrinsic or extrinsic ethnic factors that may affect the efficacy of tafamidis. Therefore, the participation of Japanese patients in Study B3461028, a global clinical study, was appropriate. However, the number of Japanese patients enrolled in Study B3461028 was very small, precluding adequate assessment of the consistency in study results between the Japanese subpopulation and the entire study population. The deaths of Japanese patients only in the tafamidis group is an important outcome to be noted in the primary endpoint of Study B3461028. However, a cardiovascular-related death occurred in only 1 of these patients, and the deaths of 3 Japanese patients are not necessarily signaling a particular concern about the efficacy of tafamidis in Japanese patients. Within the Japanese subpopulation, the frequency of cardiovascular-related hospitalizations was lower in the pooled tafamidis group than in the placebo group, and the declines from baseline in distance walked during 6-minute walk test and KCCQ-OS score at Month 30 (secondary endpoints) were smaller in the pooled tafamidis group than in the placebo group. These results of endpoints suggest similarity in the efficacy of tafamidis between the Japanese subpopulation and the entire study population. Furthermore, the data of individuals in Japanese subpopulation also suggest comparable efficacy of tafamidis expected between Japanese and non-Japanese patients. Meanwhile, although Study B3461028 enrolled no Japanese patients with variant ATTR-CM, this patient population should also be included in the intended population for the treatment with tafamidis, based on the results from the entire study population of Study B3461028, and for the following reasons: (1) There have been no identified differences that may affect the efficacy of tafamidis, in intrinsic or extrinsic ethnic factors including the PK and PD of tafamidis, medical environment, and pathology of ATTR-CM between Japanese and non-Japanese patients; and (2) ATTR-CM is a rare, progressive, and ultimately fatal disease, for which there are no effective therapeutic agents, and tafamidis is medically much needed. The appropriateness of the above discussion will be finalized, after also taking into account the comments from the Expert Discussion.

7.R.3 Safety

Based on the discussions in Sections 7.R.3.1 to 7.R.3.3 below, PMDA has concluded that tafamidis has acceptable safety in patients with ATTR-CM and that no additional precautions are necessary for the use of tafamidis in patients with ATTR-CM at present, because of no new safety concerns or no adverse events increasing dose-dependently as compared with the previous application for the initial approval, and based on the efficacy of tafamidis in the treatment of ATTR-CM, as demonstrated in Study B3461028.

7.R.3.1 Adverse events requiring attention

The applicant's explanation about the events requiring attention identified during the review for the initial approval (hepatic disorders, hypersensitivity reactions, infections, and gastrointestinal disorders) and the possible effects of tafamidis on thyroid function based on its mechanism of action:

No new safety concerns were identified in the reviews of the adverse events occurring in Study B3461028 [Sections 7.R.3.1.1 to 7.R.3.1.5] or the post-marketing information from patients treated with tafamidis for ATTR-PN in and outside Japan (November 16, 2011 to May 15, 2018).[9)] Therefore, the incidences of adverse reactions related to the attention-requiring events will be presented in the package insert as done for the approved indication, and no additional cautionary advice will be necessary.

PMDA's view:

The summaries of the attention-requiring adverse events in Sections 7.R.3.1.1 to 7.R.3.1.5 reveal no new safety concerns or no adverse events tending to increase dose-dependently as compared with the approved indication. Thus, the existing cautionary advice remains valid for continuous appropriate safety measures. In addition, no new safety concerns have been identified in the occurrence of adverse events in Study B3461028 or in post-marketing information from patients with ATTR-PN treated with tafamidis in Japan or overseas.

7.R.3.1.1 Hepatic disorders

In Study B3461028, the incidences of hepatic disorder-related events[10)] were 22.0% (39 of 177 patients) in the placebo group, 26.1% (23 of 88 patients) in the tafamidis 20 mg group, and 22.2% (39 of 176 patients) in the tafamidis 80 mg group. No patient died from a hepatic disorder-related event. The incidences of serious hepatic disorder-related events were 0.6% (1 of 177 patients) in the placebo group, 5.7% (5 of 88 patients) in the tafamidis 20 mg group, and 1.1% (2 of 176 patients) in the tafamidis 80 mg group. A causal relationship to the study drug was ruled out for all events except moderate liver function test increased in 1 patient in the tafamidis 80 mg group observed on Day 94 of treatment. However, the treatment with the study drug was continued, and the event resolved. No patients discontinued the study due to hepatic disorder-related events. There were no marked changes from baseline in liver function test parameters (ALT, AST, bilirubin, and γ-GTP) throughout the study period either in the placebo group or tafamidis groups.

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9) The total exposure was 4783 patient-years.

10) A Standardized MedDRA query (SMQ) in Medical dictionary for regulatory activities (MedDRA) "Drug related hepatic disorders - comprehensive search (narrow)"

7.R.3.1.2 Hypersensitivity reactions

In Study B3461028, the incidences of hypersensitivity-related events[11] were 44.6% (79 of 177 patients) in the placebo group, 31.8% (28 of 88 patients) in the tafamidis 20 mg group, and 35.2% (62 of 176 patients) in the tafamidis 80 mg group. One patient in the placebo group (Stevens-Johnson syndrome) and 1 patient in the tafamidis 80 mg group (dyspnoea) died from hypersensitivity-related events. However, a causal relationship to the study drug was ruled out for both events. The incidences of serious hypersensitivity-related events were 5.6% (10 of 177 patients) in the placebo group, 2.3% (2 of 88 patients) in the tafamidis 20 mg group, and 4.0% (7 of 176 patients) in the tafamidis 80 mg group. With the exception of dyspnea in 1 patient in the placebo group, a causal relationship to the study drug was ruled out for all events. Hypersensitivity-related events led to study discontinuation in 1.1% (2 of 177) of patients in the placebo group and 0.6% (1 of 176) of patients in the tafamidis 80 mg group. However, a causal relationship to the study drug was ruled out for all these events. Most of the hypersensitivity-related events for which a causal relationship to tafamidis could not be ruled out developed after a long interval from the start of treatment with tafamidis and resolved during the treatment.

7.R.3.1.3 Infections

In Study B3461028, no patients died from infection-related events.[12] The incidences of serious infection-related events were 20.9% (37 of 177 patients) in the placebo group, 21.6% (19 of 88 patients) in the tafamidis 20 mg group, and 18.2% (32 of 176 patients) in the tafamidis 80 mg group. A causal relationship to the study drug was ruled out for all events except severe urinary tract infection in 1 patient in the tafamidis 80 mg group observed on Day 377. The patient experiencing severe urinary tract infection continued treatment with the study drug and the event resolved. Serious infection-related events led to study discontinuation in 2.3% (4 of 177) of patients in the placebo group, 2.3% (2 of 88) of patients in the tafamidis 20 mg group, and 3.4% (6 of 176) of patients in the tafamidis 80 mg group. However, a causal relationship to the study drug was ruled out for all events. The incidences of urinary tract infection-related events[13] were 16.9% (30 of 177 patients) in the placebo group, 11.4% (10 of 88 patients) in the tafamidis 20 mg group, and 12.5% (22 of 176 patients) in the tafamidis 80 mg group. There were no vaginal infection-related events.[14]

7 R.3.1.4 Gastrointestinal disorders

In Study B3461028, the incidences of diarrhoea-related events[15] were 22.0% (39 of 177 patients) in the placebo group, 11.4% (10 of 88 patients) in the tafamidis 20 mg group, and 14.2% (25 of 176 patients) in the tafamidis 80 mg group. The most commonly reported diarrhoea-related events was diarrhoea. The incidences of diarrhoea were 22.0% (39 of 177 patients) in the placebo group, 11.4% (10 of 88 patients) in the tafamidis 20 mg group, and 12.5% (22 of 176 patients) in the tafamidis 80 mg group. Serious diarrhoea-related events occurred only in the placebo group at the incidence of 0.6% (1 of 177 patients). The incidences of abdominal

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[11] MedDRA SMQs "Hypersensitivity (narrow)," "Asthma/bronchospasm (broad and narrow)"; MedDRA PTs "Apnoea ,"Apnoeic attack," "Dyspnoea," "Dyspnoea at rest," "Dyspnoea exertional," "Dyspnoea paroxysmal nocturnal," "Hypoventilation," "Irregular breathing," "Nocturnal dyspnoea," "Orthopnoea," "Respiration abnormal," "Respiratory distress," and "Upper airway resistance syndrome"

[12] MedDRA System organ class (SOC) "Infections and infestations"

[13] MedDRA HLTs "Genitourinary tract infections and inflammations NEC" and "Urinary tract infections"

[14] MedDRA HLT "Vaginal and vulval infections and inflammations"

[15] MedDRA SMQ "Noninfectious diarrhoea (narrow)"

pain-related events[16] were 9.6% (17 of 177 patients) in the placebo group, 9.1% (8 of 88 patients) in the tafamidis 20 mg group, and 8.5% (15 of 176 patients) in the tafamidis 80 mg group. The most commonly reported abdominal pain-related event was abdominal pain. The incidences of abdominal pain were 5.1% (9 of 177 patients) in the placebo group, 6.8% (6 of 88 patient) in the tafamidis 20 mg group, and 5.7% (10 of 176 patients) in the tafamidis 80 mg group. Serious abdominal pain-related events were reported in 2.3% (4 of 177) of patients in the placebo group, 3.4% (3 of 88) of patients in the tafamidis 20 mg group, and 1.1% (2 of 176) of patients in the tafamidis 80 mg group. However, a causal relationship to the study drug was ruled out for all these events.

7.R.3.1.5 Possible effects on thyroid function

In Study B3461028, the incidences of thyroid dysfunction-related events[17] were 10.7% (19 of 177 patients) in the placebo group, 6.8% (6 of 88 patients) in the tafamidis 20 mg group, and 9.1% (16 of 176 patients) in the tafamidis 80 mg group. The commonly reported thyroid dysfunction-related events were hypothyroidism and hyperthyroidism. The incidences of hypothyroidism were 5.6% (10 of 177 patients) in the placebo group, 5.7% (5 of 88 patients) in the tafamidis 20 mg group, and 6.8% (12 of 176 patients) in the tafamidis 80 mg group. The incidences of hyperthyroidism were 1.1% (2 of 177 patients) in the placebo group, 0% (0 of 88 patients) in the tafamidis 20 mg group, and 1.7% (3 of 176 patients) in the tafamidis 80 mg group. There were no serious thyroid dysfunction-related events or thyroid dysfunction-related events leading to study discontinuation. No clinically relevant changes from baseline were observed in any thyroid function test parameter (total T_4, free T_4, or thyroid stimulating hormone) throughout the study period in any treatment group.

7.R.3.2 Safety in the Japanese subpopulation of Study B3461028

The applicant's explanation:

The incidences of adverse events in the 17 Japanese patients enrolled in Study B3461028 were 100% (5 of 5 patients) in the placebo group, 100% (2 of 2 patients) in the tafamidis 20 mg group, and 80.0% (8 of 10 patients) in the tafamidis 80 mg group. The incidences of serious adverse events in these Japanese patients were 80.0% (4 of 5 patients) in the placebo group, 100% (2 of 2 patients) in the tafamidis 20 mg group, and 70.0% (7 of 10 patients) in the tafamidis 80 mg group. Thus, the incidences of adverse events and serious adverse events were similar among the placebo group and each tafamidis group. A total of 3 patients in the tafamidis 80 mg group discontinued the study due to adverse events. However, a causal relationship to the study drug was ruled out for all these events.

The hepatic disorder-related event[9] reported in the Japanese subpopulation was hypoprothrombinaemia (1 patient in the placebo group). Hypersensitivity-related events[10] reported in the Japanese subpopulation were asthma (1 patient in the tafamidis 80 mg group), dermatitis contact (1 patient in the tafamidis 80 mg group), eczema (1 patient in the tafamidis 80 mg group), rash (1 patient each in the placebo group and the tafamidis 80 mg group), and urticaria (1 patient each in the tafamidis 20 mg group and the tafamidis 80 mg group). Serious infection-related events[11] reported in the Japanese subpopulation included gastroenteritis (1 patient in the

[16] MedDRA HLT "Gastrointestinal and abdominal pains (excluding oral and throat)"
[17] MedDRA SMQ "Thyroid dysfunction (broad and narrow)"

tafamidis 80 mg group), pneumonia (1 patient each in the placebo group, the tafamidis 20 mg group, and the tafamidis 80 mg group), and subcutaneous abscess (1 patient in the tafamidis 80 mg group). Urinary tract infection-related events[12)] reported in the Japanese subpopulation were cystitis (3 patients in the tafamidis 80 mg group) and urinary tract infection (1 patient in the tafamidis 80 mg group). No vaginal infection-related events[13)] were reported in the Japanese subpopulation. The diarrhoea-related event[14)] reported in the Japanese subpopulation was diarrhoea (1 patient in the tafamidis 20 mg group). The abdominal pain-related event[15)] reported in the Japanese subpopulation was abdominal pain (1 patient in the tafamidis 80 mg group). The thyroid dysfunction-related event[16)] reported in the Japanese subpopulation was hypothyroidism (4 patients in the placebo group). Serious gastroenteritis and subcutaneous abscess were reported only in Japanese patients, and a causal relationship to the study drug was ruled out for both events. Thus, the safety profile of tafamidis did not tend to differ substantially between the Japanese subpopulation and the entire study population. In addition, a subgroup analysis based on the patient characteristics that differed between the Japanese subpopulation and the entire study population (wild-type vs variant; > vs ≤ median body weight; > vs ≤ median BMI) showed no large differences in the safety of tafamidis between the subgroups by each patient characteristic.

PMDA's view:

Due to the small number of Japanese patients enrolled in Study B3461028, it is difficult to draw a concrete conclusion on the differences in the safety profile of tafamidis between Japanese and non-Japanese patients based on the study results. Nonetheless, there were no substantial differences in the occurrence of adverse events between the Japanese subpopulation and the entire study population of Study B3461028, and based on the study results, tafamidis has acceptable safety not only in the entire study population but also in Japanese subpopulation. Despite limited safety data from Japanese patients with ATTR-CM treated with tafamidis, the usual dose of tafamidis for the treatment of ATTR-CM was determined as 80 mg, which is considerably higher than the approved dose for ATTR-PN. The applicant should continue to collect safety data of tafamidis in the post-marketing setting and appropriately communicate new findings to healthcare professionals.

7.R.3.3 Safety information from ongoing clinical studies

The applicant's explanation:

Table 23 shows the incidences of adverse events in ongoing clinical studies (Studies B3461026[18)] and B3461045[19)]).

[18)] Study B3461026 is an open-label, uncontrolled study in 31 non-Japanese patients with ATTR-CM who successfully completed Study B3461025, to evaluate the long-term safety and efficacy of tafamidis (ongoing since September 2009; data cutoff on August 1, 2018). Patients received repeated oral doses of tafamidis 20 mg once daily. The duration of treatment is 10 years or until tafamidis is marketed. As of the data cutoff, the duration of treatment (median [range]) was 31.8 [4.0, 104.4] months.

[19)] Study B3461045 is a global, randomized, double-blind study in 252 Japanese or non-Japanese patients with ATTR-CM, who successfully completed Study B3461028, to evaluate the long-term safety of tafamidis (ongoing since June 2016; data cutoff on August 1, 2018). Patients who had received tafamidis at 20 mg or 80 mg in Study B3461028 continued the same dose, while patients who had received placebo in Study B3461028 were assigned to either tafamidis 20 mg or 80 mg. Tafamidis was orally administered once daily. The duration of treatment is 60 months or until tafamidis is marketed. As of the data cutoff, the duration of treatment (median [range]) was 9.0 [0.0, 25.1] months.

Table 23. Incidences of adverse events in ongoing clinical studies

	Study B3461026	Study B3461045			
Adverse events	Tafamidis 20 mg (N = 31)	Placebo /tafamidis 20 mg[a] (N = 28)	Placebo /tafamidis 80 mg[a] (N = 54)	Tafamidis 20 mg/ tafamidis 20 mg[a] (N = 60)	Tafamidis 80 mg/ tafamidis 80 mg[a] (N = 110)
Adverse events	100 (31)	100 (28)	90.7 (49)	90.0 (54)	85.5 (94)
Adverse events resulting in death	74.2 (23)	7.1 (2)	3.7 (2)	1.7 (1)	1.8 (2)
Serious adverse events	90.3 (28)	78.6 (22)	53.7 (29)	50.0 (30)	46.4 (51)
Adverse events leading to study discontinuation	54.8 (17)	21.4 (6)	7.4 (4)	10.0 (6)	5.5 (6)

% (n)
a, Group assigned in Study B3461028/group assigned in Study B3461045
Adverse events that occurred during Study B3451026 or B3461045 in which patients were enrolled after the completion of Study B3461025 or B3461028 are summarized.

Adverse events resulting in death in ≥2 patients during Study B3461026, which followed Study B3461025, were congestive cardiac failure (19.4% [6 of 31 patients]) and familial amyloidosis (12.9% [4 of 31 patients]). Serious adverse events reported with an incidence of ≥10% were congestive cardiac failure (29.0%, [9 of 31 patients]), cardiac failure (19.4% [6 of 31 patients]), and familial amyloidosis (12.9% [4 of 31 patients]). There were no adverse events leading to study discontinuation with an incidence of ≥10%.

Adverse events resulting in death occurring during Study B3461045, which followed Study B3461028 were chronic cardiac failure and congestive cardiac failure in 1 patient each in the placebo/tafamidis 20 mg group (Study B3461028/Study B3461045), pneumonia and sepsis in 1 patient each in the placebo/tafamidis 80 mg group, completed suicide in 1 patient in the tafamidis 20 mg/tafamidis 20 mg group, and multiple organ dysfunction syndrome and craniocerebral injury in 1 patient each in the tafamidis 80 mg/tafamidis 80 mg group. A causal relationship to the study drug was ruled out for all these events. Serious adverse events reported with an incidence of ≥10% in any treatment group were cardiac failure (17.9% [5 of 28] of patients in the placebo/tafamidis 20 mg group, 11.1% [6 of 54] of patients in the placebo/tafamidis 80 mg group, 6.7% [4 of 60] of patients in the tafamidis 20 mg/tafamidis 20 group, and 10.9% [12 of 110] of patients in the tafamidis 80 mg/tafamidis 80 mg group) and congestive cardiac failure (21.4% [6 of 28 patients], 5.6% [3 of 54 patients], 5.0% [3 of 60 patients], and 2.7% [3 of 110 patients]). A causal relationship to the study drug was ruled out for all these events. There were no adverse events leading to study discontinuation with an incidence of ≥10% in any treatment group.

Thus, no new safety concerns for the long-term safety of tafamidis have been identified in Studies B3461026 and B3461045.

PMDA has accepted the applicant's explanation.

7.R.4 Indication and intended patient population

The applicant's explanation about the selection of patients with ATTR-CM to be treated with tafamidis:
ATTR-CM is confirmed based on clinical symptoms, examinations (e.g., hematological test,

echocardiography, myocardial scintigraphy, cardiac MRI), TTR-derived amyloid deposits by Congo Red staining and immunohistochemical staining in biopsy tissues (e.g., myocardium, gastric mucosa, rectal mucosa, abdominal wall fat), and a TTR gene mutation (Clinical Practice Guideline for Amyloidosis). In the clinical studies of tafamidis in patients with ATTR-CM, eligible patients were also selected according to these diagnostic criteria. The proposed indication of tafamidis in the present application was defined based on the target patient population and the endpoints of the clinical studies. In view of the importance to select patients to be treated with tafamidis therapy according to the latest Japanese guidelines, etc., the package insert should advise that tafamidis be administered to patients with confirmed transthyretin amyloidosis according to the guidelines, etc. in the "Precautions for Indications" section.

PMDA's view:
It is important that patients to be treated with tafamidis have extracellular deposition of TTR-derived amyloid histopathologically confirmed by biopsy tissues, a finding suggestive of cardiac amyloidosis on diagnostic images, and clinically relevant cardiac failure likely attributable to cardiac amyloidosis. In addition, as discussed in Section "7.R.2 Efficacy," tafamidis may be used for patients with ATTR-CM, regardless of disease type or TTR genotype, including those suffering NYHA class ≥III cardiac failure. Accordingly, Indications and Precautions for Indications should be defined as below. Study B3461028 was conducted in patients who had a history of cardiac failure with ≥1 related hospitalization or had ongoing cardiac failure with volume overload or elevated intracardiac pressures treated with a diuretic agent, and this should be properly communicated through the package insert. The descriptions of indications and precautions for indications will be finalized taking into account comments from the Expert Discussion.

Indications (proposed by PMDA)
Transthyretin amyloid cardiomyopathy (wild-type or variant)

Precautions for Indications (proposed by PMDA)
Both indications
Tafamidis Meglumine should be administered to patients who have been confirmed to have transthyretin amyloidosis according to the latest Clinical Practice Guidelines for Amyloidosis.

Transthyretin amyloid cardiomyopathy (wild-type or variant)
Tafamidis Meglumine should be used for patients who have cardiac failure caused by transthyretin amyloid cardiomyopathy

7.R.5 Dosage and administration

The applicant's explanation about the use of an additional dose of 80 mg in Study B3461028 that was higher than 20 mg used in Study B3461025:
At present, there are no established surrogate markers for the clinical efficacy of a drug against tissue amyloid deposition or ATTR-CM. However, considering that the efficacy of tafamidis on ATTR-CM would depend on the stabilization of TTR tetramers, TTR percent stabilization was used as the indicator to find the optimal dose

of tafamidis in the treatment of ATTR-CM. In Study B3461025, 20 mg was used for being the approved dose for the treatment of ATTR-PN based on the results from previous clinical studies in healthy adults or patients with ATTR-PN. Subsequently, the results of Study B3461040 showed that the stabilization of TTR tetramers by tafamidis was dependent on plasma tafamidis concentration and that TTR percent stabilization nearly peaked at the dose of 80 mg [see Section "6.R.2 Rationale for the dosage regimen selected for Study B3461028"]. In Study B3461028, which assessed the 2 doses, no clear differences were seen between the tafamidis 20 mg group and the tafamidis 80 mg group, in the primary endpoint composed of all-cause mortality and the frequency of cardiovascular-related hospitalizations, its 2 individual components (i.e., all-cause mortality and frequency of cardiovascular related hospitalizations), or other key secondary endpoints (changes from baseline in the distance walked during 6-minute walk test and KCCQ-OS score at Month 30) (Tables 14 and 15). However, post-hoc analyses of biomarkers for cardiac failure or myocardial disorders (N-terminal pro-hormone brain natriuretic peptide [NT-proBNP] and troponin I) by treatment group revealed that changes from baseline in NT-proBNP and troponin I at Month 30 were smaller in the tafamidis 80 mg group than in the tafamidis 20 mg group (Table 24). As with NT-proBNP and troponin I, high levels of troponin T, a protein derived from the myocardium, are associated with deaths in patients with ATTR-CM (*Eur Heart J.* 2018;39:2799-806 and *J Am Coll Cardiol.* 2016;68:1014-20). Based on this finding, the recommended dose of tafamidis for patients with ATTR-CM should be 80 mg. The safety analyses in Study B 3461028 did not show the incidences of adverse events tending to be higher in the tafamidis 80 group than in the tafamidis 20 mg group [see Section "7.R.3 Safety"].

Table 24. NT-proBNP and troponin I levels in Study B3461028 (ITT population)

Entire study population		Placebo	Pooled tafamidis	Tafamidis 20 mg	Tafamidis 80 mg
NT-proBNP (pg/mL)	Baseline	N = 177 3845.5 ± 2971.5	N = 264 3948.7 ± 3375.9	N = 88 3963.8 ± 3904.6	N = 176 3941.1 ± 3090.0
	Month 30	N = 80 6642.4 ± 6937.0	N = 170 4397.6 ± 4733.9	N = 60 4873.7 ± 5476.9	N = 110 4137.9 ± 4279.7
	Change from baseline	N = 80 3502.2 ± 5106.8	N = 170 1248.8 ± 3449.6	N = 60 1842.9 ± 3905.8	N = 110 924.7 ± 3145.2
Troponin I (ng/mL)	Baseline	N = 176 0.178 ± 0.177	N = 264 0.275 ± 0.886	N = 88 0.308 ± 0.778	N = 176 0.259 ± 0.937
	Month 30	N = 81 0.230 ± 0.274	N = 167 0.185 ± 0.450	N = 59 0.226 ± 0.704	N = 108 0.162 ± 0.210
	Change from baseline	N = 81 0.100 ± 0.172	N = 167 0.022 ± 0.160	N = 59 0.041 ± 0.176	N = 108 0.011 ± 0.150
Japanese subpopulation		Placebo	Pooled tafamidis	Tafamidis 20 mg	Tafamidis 80 mg
NT-proBNP (pg/mL)	Baseline	N = 5 8429.0 ± 6908.2	N = 12 3132.4 ± 1690.8	N = 2 3022.0, 3417.0 [a]	N = 10 3115.0 ± 1866.4
	Month 30	N = 5 20671.5 ± 17994.4	9 3733.1 ± 3350.0	N = 2 3341.0, 7007.0 [a]	N = 7 3321.4 ± 3599.1
	Change from baseline	N = 5 12242.4 ± 12828.7	9 332.0 ± 2467.3	N = 2 319.0, 3590.0 [a]	N = 7 −131.6 ± 2469.2
Troponin I (ng/mL)	Baseline	N = 5 0.248 ± 0.063	N = 12 0.194 ± 0.069	N = 2 0.14, 0.21 [a]	N = 10 0.198 ± 0.073
	Month 30	N = 5 0.602 ± 0.327	9 0.249 ± 0.146	N = 2 0.13, 0.18 [a]	N = 7 0.276 ± 0.156
	Change from baseline	N = 5 0.354 ± 0.278	9 0.037 ± 0.102	N = 2 −0.08, 0.04 [a]	N = 7 0.053 ± 0.107

Mean ± SD
a, Values from individual patients

Although the small number of Japanese patients enrolled in Study B3461028 precludes accurate interpretation of the Study results, the results of the efficacy endpoints, including NT-proBNP and troponin I, in each treatment group in the Japanese subpopulation did not differ substantially from those in the entire study population (Tables 14, 15, and 24). In addition, the PK of tafamidis was similar in Japanese and non-Japanese healthy adults, and the relationship between TTR percent stabilization and the plasma TTR/tafamidis molar ratio was similar in Japanese and non-Japanese [see Section "6.R.1 Differences in the PK and PD of tafamidis between Japanese and non-Japanese"]. These findings suggest that tafamidis is insensitive to ethnic factors. Therefore, the recommended dosage regimen of tafamidis should be 80 mg once daily for Japanese patients with ATTR-CM as well.

PMDA asked the applicant to explain the details of patients who required dose reduction of tafamidis in Studies B3461028 and B3461045 and to reconsider the appropriate dosage regimen of tafamidis.

The applicant's explanation:
In Study B3461028, 4 patients in the placebo group and 2 patients in the tafamidis 80 mg group underwent dose reduction of the study drug. One of the 2 patients in the tafamidis 80 mg group experienced urinary tract pain (moderate, non-serious) on Day 15, resulting in dose reduction of tafamidis to 40 mg. Treatment with tafamidis was continued and the urinary tract pain resolved on Day 19. The patient was treated for 575 days. The other patient in the tafamidis 80 mg group experienced headache (moderate, non-serious) on Day 113,

resulting in dose reduction of tafamidis to 40 mg. Treatment with tafamidis was continued and the headache resolved on Day 116. The patient continued with the treatment until experiencing cardiogenic shock leading to discontinuation on Day 217, and was withdrawn from the study to undergo heart and right kidney transplantations. The survival of both patients was confirmed at Month 30, and there were no safety concerns after the dose reduction. In Study B3461045, 1 patient required dose reduction of the study drug (data cutoff on August 1, 2018). The patient received placebo in the preceding Study B3461028 and was then assigned to the tafamidis 80 mg group in Study B3461045. At Month 12, the dose of tafamidis was reduced to 20 mg due to a high γ-GTP level. However, treatment with tafamidis was ongoing as of the data cutoff date. Based on these results, the dosage and administration of tafamidis for the treatment of ATTR-CM will be modified as follows:

Dose and Administration modified by the applicant (The underlined words are added to the proposed text.)

Dosage and Administration

Transthyretin familial amyloid polyneuropathy

The usual adult dose is 20 mg of Tafamidis Meglumine administered orally once daily.

Transthyretin amyloid cardiomyopathy

The usual adult dose is 80 mg of Tafamidis Meglumine administered orally once daily. <u>The treatment should start at the dose of 80 mg, and the dose may be reduced depending on tolerability.</u>

PMDA's view:

ATTR-CM is caused by the destabilization or dissociation of TTR tetramers resulting in amyloid deposits in the myocardium, and tafamidis acts to stabilize TTR tetramers. A dose-finding study designed with a likely low-rate true endpoint (e.g., survival rate) would be practically infeasible in patients with this rare disease. The applicant decided to design Study B3461028, the sole confirmatory study involving patients with ATTR-CM, with an additional dose of >20 mg to be assessed, and it was 80 mg that the applicant selected in expectation of sufficient TTR stabilization, based on the TTR percent stabilization data referable when the study was being planned. Despite unestablished relationship between TTR percent stabilization and amyloid deposition or clinical relevance of increased TTR percent stabilization in patients with ATTR-CM at present, these applicant's decisions are justifiable to some extent. As discussed in Section "7.R.2.1 Efficacy evaluation results," it would be inevitable, in view of feasibility, to design a clinical study in which major evaluations were to be performed by comparison between the pooled tafamidis group and the placebo group. The dose level comparison, although inevitably exploratory due to the small number of patients in each dose group, yielded the following results by dose level.

Based on the primary endpoint composed of all-cause mortality and the frequency of cardiovascular-related hospitalizations at Month 30 and its each component (i.e., all-cause mortality and frequency of cardiovascular related hospitalizations) and changes from baseline in the distance walked during 6-minute walk test and KCCQ-OS score at Month 30 (secondary endpoints), clinically significant efficacy of tafamidis have been demonstrated at both 20 mg and 80 mg on the whole, with no significant differences between the doses.

Nonetheless, PMDA has concluded that the usual dose of 80 mg of tafamidis is appropriate for the treatment of ATTR-CM, based on the following points.

- Because NT-pro BNP and troponin I are essentially biomarkers for cardiac failure or myocardial disorders, measured values should be interpreted carefully. However, these biomarkers are also useful for predicting the progression and prognosis of ATTR-CM (Clinical Practice Guidelines for Amyloidosis). Considering this, the results of NT-pro BNP and troponin I from Study B3461028 suggested that tafamidis was more effective at 80 mg than at 20 mg.
- The results indicate a higher TTR stabilization at 80 mg than at 20 mg.
- ATTR-CM is progressive and ultimately fatal. Each patient should be treated at a dose that will optimize its efficacy.
- There were no substantial differences in the safety of tafamidis between 20 mg and 80 mg.
- Comparisons of the PK, PD, efficacy, and safety of tafamidis showed no clinically significant differences between Japanese and non-Japanese patients [see Sections "7.R.2.4 Efficacy in the Japanese subpopulation of Study B3461028" and "7.R.3.2 Safety in the Japanese subpopulation of Study B3461028"].

In Study B3461028, comparisons between the pooled tafamidis group and the placebo group demonstrated superiority of tafamidis to placebo in efficacy, and an exploratory analysis showed that tafamidis improved the primary endpoint composed of all-cause mortality and the frequency of cardiovascular hospitalizations at both 20 and 80 mg as compared with placebo. In addition, in view of the results of other efficacy endpoints, tafamidis is expected to have a certain level of efficacy even at 20 mg. In Studies B3461028 and B3461045, only 3 patients required dose reduction during the treatment. In 2 of these 3 patients, the adverse events leading to dose reduction resolved after the dose reduction. Furthermore, all 3 patients were able to continue treatment at the reduced dose for a certain period of time. These results suggest that dose reduction may have an advantage from the viewpoint of tolerability. In clinical settings, there are patients with various characteristics. Minimizing amyloid deposition will delay the progression of ATTR-CM that is an amyloid deposition-induced progressive disease. Therefore, tafamidis should not be discontinued without exception even when poorly tolerated, and the option to continue tafamidis at a reduced dose should be retained. PMDA has concluded that the description of dosage and administration modified by the applicant is largely acceptable. However, this conclusion will be finalized after taking into account the comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's explanation:

Because of the small number of Japanese participants in Study B3461028, the applicant will conduct a use-results survey covering all patients treated with tafamidis for ATTR-CM. The purpose of the survey is to accumulate data on the use of tafamidis in clinical practice and evaluate the safety of tafamidis. The survey will collect safety information, including data on events related to hepatic toxicity, hypersensitivity reactions, reproductive and developmental toxicity, and infections, as well as safety data of tafamidis administered to Japanese patients with severe hepatic impairment and those with variant ATTR-CM. The survey will also target patients who have been receiving tafamidis at 20 mg once daily for the treatment of ATTR-PN (the approved

indication) and will start receiving the treatment for concurrent ATTR-CM so as to obtain safety data after dose increase from 20 mg once daily to 80 mg once daily.

PMDA's view:

There were limited number of Japanese patients with ATTR-CM who participated in the clinical study. A dose of 80 mg is considerably higher than the approved dose for the treatment of ATTR-PN but was selected as the usual dose for the treatment of ATTR-CM, despite the common pathogenesis of ATTR-PN and ATTR-CM and the same action mechanism of tafamidis. There is lack or limitation of data from patients with variant ATTR-CM or advanced ATTR-CM with NYHA class ≥III cardiac failure symptoms and those requiring dose reduction of tafamidis. For these reasons, a drug use-results survey should be conducted in the post-marketing setting to accumulate data from a certain number of patients. Data including patient characteristics, safety information, etc. should be collected early in an unbiased manner from patients treated with tafamidis, and available information should be promptly provided to healthcare professionals to promote the appropriate use of tafamidis. Therefore, the drug use-results survey should cover all patients treated with tafamidis during the re-examination period to continue to collect safety data, etc. from clinical settings. Details of the post-marketing surveillance, including safety specifications and the appropriateness of risk classification, pharmacovigilance activities, and risk minimization activities will be finalized according to the Risk Management Guidance (Notification No. 0411-(1) of the Safety Division of PFSB and No. 0411-(2) of the Evaluation and Licensing Division of PFSB, both dated April 11, 2012), after discussions at the Expert Discussion.

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 inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that tafamidis has efficacy in the treatment of ATTR-CM (wild-type or variant), and that tafamidis has acceptable safety in view of its benefits. Tafamidis is clinically meaningful because it offers a new therapeutic option for patients with ATTR-CM (wild-type or variant). The indication, dosage and administration, and post-marketing investigation items should be further discussed.

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

Review Report (2)

February 8, 2019

Product Submitted for Approval

Brand Name	Vyndaqel Capsules 20 mg
Non-proprietary Name	Tafamidis Meglumine
Applicant	Pfizer Japan Inc.
Date of Application	November 2, 2018

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 Sections "7.R.1 Clinical positioning of tafamidis," "7.R.3 Safety," and "7.R.5 Dosage and administration" as described in Review Report (1).

PMDA also discussed the following points and took action as necessary.

1.1 Efficacy and intended patient population

All the PMDA's conclusions presented in Sections "7.R.2 Efficacy" and "7.R.4 Indication and intended patient population" in Review Report (1) were supported by the expert advisors, except those on efficacy by severity of cardiac failure.

The expert advisors' comments on the efficacy of tafamidis by severity of cardiac failure:

- The frequency of cardiovascular-related hospitalizations (a component of the primary endpoint) in surviving patients at Month 30 was higher in the pooled tafamidis group than in the placebo group within the subgroup of patients with NYHA class III. This outcome is noteworthy.
- Within the subgroup of patients with NYHA class III, cardiovascular-related mortality at Month 30 was similar between the pooled tafamidis group and the placebo group. The capability of tafamidis in this patient population to prevent cardiovascular-related death is questionable.

- In the subgroup of patients with NYHA class I or II, the survival rate at Month 30 and the frequency of cardiovascular-related hospitalizations at Month 30 (the individual components of the primary endpoint), as well as cardiovascular-related mortality at Month 30, were consistently favorable in the pooled tafamidis group as compared with the placebo group. The above results in the subgroup of patients with NYHA class III, who had more advanced cardiac failure, were quite consistent with the mechanism of action of tafamidis that inhibits the formation of new TTR amyloid fibrils.
- The efficacy and safety of tafamidis remain unknown in patients with NHYA class IV, because this patient population was excluded from Study B3461028. However, tafamidis is likely to be less effective in these patients.
- In general, severer cardiac failure requires medication. However, patients with cardiac failure at or above a certain level of severity may be poorly responsive to tafamidis. For patients in this population, whether to treat with tafamidis should be determined on this understanding.
- Based on the above, whether tafamidis should be used for the treatment of patients with NYHA class ≥III should be considered carefully.

Taking account of the above comments, the Expert Discussion had further discussion. ATTR-CM is a progressive disease having no alternative treatment options. The NYHA classification does not have clear-cut boundaries between classes. Cardiac failure may worsen or improve during tafamidis therapy. These factors and the study results summarized below indicate that tafamidis has promising clinically significant efficacy in patients with NYHA class III, although not to the extent in those with less severe cardiac failure. Accordingly, PMDA has concluded that tafamidis therapy should be made available for patients with NYHA class ≥III as well, with appropriate cautions noted.

- In the NYHA classification-based subgroup analyses in Study B3461028, Finkelstein-Schoenfeld scores for the primary endpoint were favorable (>0) in the pooled tafamidis group as compared with the placebo group in both NYHA class I or II subgroup and III subgroup, although the difference between the pooled tafamidis group and the placebo group was smaller in NYHA class III than in class I or II.
- Six-minute walk distance and KCCQ score (secondary endpoints) results were favorable in the pooled tafamidis group as compared with the placebo group in both NYHA class subgroups.
- NT-proBNP (an exploratory endpoint) results were better in the tafamidis 80 mg than in the placebo group in both NYHA class subgroups.

Meanwhile, the package insert should present the results of the subgroup analyses by NYHA class in Study B3461028 in the “Clinical Studies” section, along with cautionary notes in the “Precautions for Indications” section as shown below. Written materials for healthcare professionals should fully inform of efficacy by severity of cardiac failure in detail as well as other knowledge, including advice on appropriate diagnosis of ATTR-CM and the presence or absence of concurrent cardiac failure and its severity, to help select appropriate patients for tafamidis therapy properly.

Precautions for Indications (additions to the text in Review Report (1))

- Tafamidis may be relatively less effective in patients with NYHA class III than in those with NYHA I or II. Whether tafamidis be used for patients with NYHA class III should be determined based on a full understanding of the mechanism of action of tafamidis and the correlation between NYHA class and efficacy suggested in clinical studies, with due consideration of the patient's condition.
- The efficacy and safety of tafamidis in patients with NYHA class IV have not been established (no experience in clinical studies).

1.2 Risk management plan (draft)

Based on the discussion presented in Section "7.R.6 Post-marketing investigations" in Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the safety specification itemized in Table 25 should be included in the present draft risk management plan for tafamidis, and that the additional pharmacovigilance activities and risk minimization activities listed in Table 26 for the new indication and the drug-use-results survey summarized in Table 27 should be conducted.

Table 25. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Hepatotoxicity • Hypersensitivity reactions • Infections • Reproductive and developmental toxicity	• Safety in patients with severe hepatic impairment • Administration to patients with mutations (ATTR-CM)
Efficacy specification		
• Efficacy in patients with mutations other than V30M (ATTR-PN) • Efficacy in Stage 2 and 3 patients (ATTR-PN) • Efficacy in post-liver transplant patients (ATTR-PN) • Long-term (≥1 year) efficacy (ATTR-PN)		

Table 26. Summary of additional pharmacovigilance activities and risk minimization activities for the new indication included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	• Dissemination of data gathered during the early post-marketing phase vigilance

Table 27. Outline of use-results survey (draft)

Objective	To evaluate the safety and other aspects of tafamidis in clinical practice
Survey method	Central registration system (all-case surveillance)
Population	Patients with ATTR-CM (wild-type or variant)
Observation period	30 months
Planned sample size	300 patients
Main survey items	Occurrence of hepatotoxicity, hypersensitivity reactions, infections, and other events, safety in patients with variant ATTR-CM, etc.

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

2.1 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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of

Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. 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 conditions of approval. The present application is intended for an orphan drug. Therefore, the re-examination period for the indication, and dosage and administration is 10 years.

Indications

Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy
Transthyretin amyloid cardiomyopathy (wild-type or variant)

Dosage and Administration

Transthyretin familial amyloid polyneuropathy
The usual adult dose is 20 mg of Tafamidis Meglumine administered orally once daily.
Transthyretin amyloid cardiomyopathy
The usual adult dose is 80 mg of Tafamidis Meglumine administered orally once daily. The dose may be reduced depending on tolerability.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Due to very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are accumulated, to understand the characteristics of patients treated with the product and promptly collect the safety and efficacy data of the product, so as to take necessary measures to ensure the proper use of the product.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin familial amyloid polyneuropathy
AUC	Area under the concentration–time curve of the analyte in plasma
$AUC_{0\text{-}inf}$	AUC from time zero to infinity
$AUC_{0\text{-}t}$	AUC from time zero to time t
AUC_{τ}	AUC during a dosing interval
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSA	Bovine serum albumin
CI	Confidence interval
CL/F	Apparent total clearance
Clinical Practice Guidelines for Amyloidosis	Saishin Amiroidoshisu no Subete (All about Amyloidosis. Latest edition.); Ishiyaku Publishers, Inc.; 2017
C_{max}	Maximum concentration of analyte in plasma
C_{min}	Minimum concentration of analyte in plasma
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
EC_{50}	Half maximal effective concentration
E_{max}	Maximum response
FOI	Fraction of initial
γ-GTP	γ-glutamyltransferase
IC_{50}	Half maximal inhibitory concentration
Ig	Immunoglobulin
ITT	Intent-to-treat
ka	Absorption rate constant
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Summary
KLH	Keyhole limpet hemocyanin
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
MATE	Multidrug and toxin extrusion protein
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NONMEM	Nonlinear mixed effect modeling
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	Quaque die
Q/F	Apparent intercompartmental clearance
SD	Sprague Dawley
SMQ	Standardized MedDRA query

SOC	System organ class
$t_{1/2}$	Half-life
T_4	Thyroxine
TDAR	T-cell dependent antibody response
t_{max}	Time to reach the maximum plasma concentration
TPGS	d-alpha-tocopheryl polyethylene glycol 1000 succinate
TSH	Thyroid stimulating hormone
TTR	Transthyretin
UGT	Uridine 5'-diphospho-glucuronosyltransferase
V_c/F	Apparent volume of distribution in central compartment
V_p/F	Apparent volume of distribution in peripheral compartment