Report on the Deliberation Results

September 2, 2013

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

[Brand name]	Vyndaqel Capsules 20 mg
[Non-proprietary name]	Tafamidis Meglumine (JAN*)
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	February 13, 2013

[Results of deliberation]
In the meeting held on August 22, 2013, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Condition for approval]
Due to the very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey, which will cover all patients treated with the product, during the re-examination period, in order to obtain the background information of patients treated with the product, and at the same time to collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

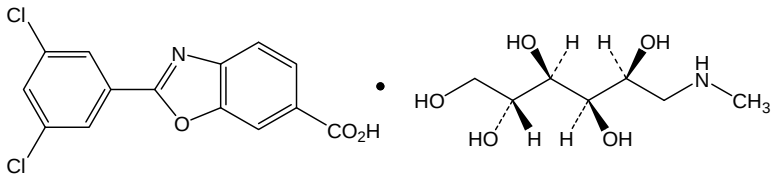
**Japanese Accepted Name (modified INN)*

Review Report

August 8, 2013
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Vyndaqel Capsules 20 mg
[Non-proprietary name] Tafamidis Meglumine
[Name of applicant] Pfizer Japan Inc.
[Date of application] February 13, 2013
[Dosage form/Strength] Each soft capsule contains 20 mg of Tafamidis Meglumine.
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Molecular formula: $C_{14}H_7Cl_2NO_3 \cdot C_7H_{17}NO_5$
Molecular weight: 503.33
Chemical name:
2-(3,5-Dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid mono (1-deoxy-1-methylamino-D-glucitol)

[Items warranting special mention]
Orphan drug (Designation [23 Drug] No.259, PFSB/ELD Notification No.1214-1 dated December 14, 2011)
[Reviewing office] Office of New Drug III

Review Results

August 8, 2013

[Brand name] Vyndaqel Capsules 20 mg
[Non-proprietary name] Tafamidis Meglumine
[Name of applicant] Pfizer Japan Inc.
[Date of application] February 13, 2013

[Results of review]
Based on the submitted data, the efficacy of the product in delaying peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy has been suggested and its safety is considered acceptable in view of its observed benefits. The occurrence of adverse events related to hepatotoxicity, hypersensitivity, reproductive and developmental toxicity, and immunotoxicity; safety in patients with severe hepatic impairment; efficacy in patients with non-V30M mutations, Stages 2 and 3 patients, and post-liver transplant patients; the long-term efficacy of tafamidis (including long-term prognosis), etc. need to be further investigated via post-marketing surveillance.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following condition.

[Indication]
Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy

[Dosage and administration]
The usual adult dose is 20 mg of Tafamidis Meglumine orally once daily.

[Condition for approval]
Due to the very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey, which will cover all patients treated with the product, during the re-examination period, in order to obtain the background information of patients treated with the product, and at the same time to collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

Review Report (1)

June 28, 2013

I. Product Submitted for Registration

[Brand name] Vyndaqel Capsules 20 mg
[Non-proprietary name] Tafamidis Meglumine
[Name of applicant] Pfizer Japan Inc.
[Date of application] February 13, 2013
[Dosage form/Strength] Each soft capsule contains 20 mg of Tafamidis Meglumine.
[Proposed indication] Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy
[Proposed dosage and administration]
The usual adult dose is 20 mg of Tafamidis Meglumine orally once daily.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or background of discovery and usage conditions in foreign countries etc.

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a particular type of amyloidosis characterized by deposition of insoluble fibrillar proteins (amyloid) derived from transthyretin (TTR) in the nerves, leading to neuropathy, and TTR transports thyroxine (T_4) and the retinol-retinol binding protein complex in the body (Ando Y, et al. *Rare/Intractable Disease Project supported by the Health and Labour Sciences Research Grant: Amyloidosis Research Committee, 2010 Clinical Practice Guideline for Amyloidosis*. 2010;20-26). The typical age of onset is the 30s to 60s. Sensory, motor, and autonomic neuropathy progresses from distal to proximal and death comes on average 3 to 15 years following symptom onset. In addition to wild-type TTR having a normal amino acid sequence, there are variants of TTR that are particularly more susceptible to misfolding, aggregation, and tissue disposition. It is known that humans with mutations in the TTR gene are more likely to develop amyloidosis such as TTR-FAP. Based on the results of the 2003 to 2005 clinical surveies conducted under the Research Project on Treatment of Intractable Diseases designated by the Ministry of Health, Labour and Welfare, the estimated prevalence of TTR-FAP in Japan is 0.87 to 1.1 per 1 million population (the Japanese population of patients is estimated at approximately 111-140) (Motozaki Y, et al. *Journal of Clinical and Experimental Medicine.* 2009;229:357-362, Kato-Motozaki Y, et al. *J Neurol Sci*. 2008;270:133-140).

The active substance Tafamidis Meglumine (tafamidis) is a benzoxazole derivative developed at FoldRx Pharmaceuticals (the US) (currently, Pfizer Inc.). It is a drug that binds to tetrameric TTR in plasma and inhibits dissociation into monomers, thereby preventing the misfolding, aggregation, and tissue deposition of TTR. In Europe, tafamidis was approved for “the treatment of transthyretin amyloidosis in adult patients with stage 1

symptomatic polyneuropathy to delay peripheral neurologic impairment" in November 2011. In the US, the Food and Drug Administration (FDA) concluded that [redacted] and issued a decision to refuse to approve tafamidis in June 2012. Pfizer is discussing with the FDA a potential path forward [see "4.(iii).B.(2).1).(c) Details of regulatory review in the US" for details].

In Japan, a clinical study was initiated in November 2011. Claiming that the results from Japanese and foreign clinical studies have shown the efficacy and safety of tafamidis indicated for "delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy," the applicant has submitted a marketing application for tafamidis.

Tafamidis Meglumine was designated as an orphan drug as of December 14, 2011 (Designation [23 Drug] No.259, PFSB/ELD Notification No.1214-1 dated December 14, 2011).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to pink powder and has been characterized by description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, polymorphism, and optical rotation. Although one crystalline form and an amorphous form of the drug substance have been detected by X-ray powder diffraction, it has been confirmed that the crystalline form is produced by [redacted] operation.

The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet-visible spectroscopy (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and mass spectrometry (MS).

Although genotoxic impurities ([redacted] and [redacted]) form during drug substance production, the levels of these impurities in the drug substance are well below the Threshold of Toxicological Concern (TTC) and both are controlled below the limit of detection ([redacted] and [redacted] ppm, respectively). Thus, the applicant has concluded that there is no risk of genotoxicity.

2.A.(1).2) Manufacturing process

The drug substance is synthesized, starting from Compound A, [redacted], and [redacted]. [redacted] step for Compound A, [redacted] step for [redacted] and [redacted], and [redacted] step for the drug substance have been defined as critical steps. The action limits have been established for the following critical process intermediates: [redacted], [redacted], [redacted] and [redacted].

2.A.(1).3) Control of drug substance

The drug substance specification includes content, description (appearance), identification (IR), purity ([redacted], heavy metals, related substances [liquid chromatography (HPLC)], residual solvents [gas chromatography]), residue on ignition, [redacted], meglumine content (HPLC), and assay (HPLC).

In the course of regulatory review, water content was added to the specification, taking also account of the specification established for the drug substance overseas.

2.A.(1).4) Stability of drug substance

The results of stability studies on the drug substance were as shown in Table 1 and the drug substance was stable during the storage period. The drug substance was photostable in a photostability study.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	Former process/3 production batches	25°C	60% RH	Double polyethylene bags + fiber drum	36 months
	New process[a)]/1 pilot batch				12 months
	New process[a)]/2 production batches[b)]				24 months
Accelerated	Former process/3 production batches	40°C	75% RH		6 months
	New process[a)]/1 pilot batch				6 months
	New process[a)]/2 production batches[c)]				6 months

a) The proposed commercial manufacturing process. To [redacted], the process parameters have been changed from those of the former process.
b) The 9-month data have been submitted for 1 batch.
c) The 8-month data have been submitted for 1 batch.

Based on the above, a re-test period of 36 months has been proposed for the drug substance when stored in double polyethylene bags in a fiber drum at room temperature.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a white to light yellow soft capsule containing 20 mg of Tafamidis Meglumine and the excipients are Macrogol 400, sorbitan monooleate, Polysorbate 80, gelatin, glycerin, D-sorbitol-sorbitan solution, and Opatint White. Since the drug substance showed poor solubility, in order to better control the particle size of the drug substance, [redacted] step was added to the production of the drug substance during development and it has been confirmed that there are no major differences in the dissolution profile etc. between the pre-change and post-change drug product. Some of foreign clinical studies were conducted with hard capsule and oral solution formulations whose bioequivalence with the proposed commercial formulation has not been demonstrated.

2.A.(2).2) Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], [redacted], and packaging/labeling/testing/storage.

2.A.(2).3) Control of drug product

The drug product specification includes strength, description (appearance), identification (HPLC, UV), purity (degradation products [HPLC]), water content, uniformity of dosage units (content uniformity test), dissolution,

and assay (HPLC).

2.A.(2).4) Stability of drug product

The results of stability studies on the drug product were as shown in Table 2. After [redacted] months of storage at the accelerated condition, decreased [redacted] was observed, which failed to meet the specification. Also for 1 production batch tested at the intermediate storage condition, decreased [redacted] was observed after [redacted] months of storage, which failed to meet the specification. The stability results of long-term studies were within the specifications. The drug product was photolabile in a photostability study.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot batches[a)]	25°C	60% RH	Laminated films[c)]/aluminum foils	24 months
	3 production batches[b)]				18 months
Intermediate	3 pilot batches[a)]	30°C	65% RH		24 months
	3 production batches[b)]				18 months
Accelerated	3 pilot batches[a)]	40°C	75% RH		6 months
	3 production batches				6 months

a) Drug substance batches produced via the former process were used.
b) The 18-, 12-, and 6-month data have been submitted, respectively.
c) The films consist of [redacted], [redacted], and [redacted] from the inside to the outside.

Based on the above, a shelf-life of 24 months has been proposed for the drug product when packaged in a laminated film/an aluminum foil (primary packaging) and stored at room temperature, protected from light.

2.B Outline of the review by PMDA

2.B.(1) Hardening of the capsule shell and addition of digestive enzymes to dissolution medium

PMDA asked the applicant to explain the reason for deciding that if the drug product fails the dissolution test, a second dissolution test will be performed using the medium containing digestive enzymes.

The applicant explained as follows:

Generally in gelatin capsules, gelatin crosslinking with excipients occurs over time during storage, resulting in the hardening of the capsule shell and delayed dissolution. As it has been reported that the bioavailability of the drug from gelatin capsules with up to a certain degree of crosslinking is not significantly altered (Digenis GA, et al. *J Pharm Sci*. 1994;83:915-921), the United State Pharmacopeia (USP) allows capsules to undergo a second dissolution test using the medium containing digestive enzymes if the capsules show a decrease in dissolution rate with time and do not pass the dissolution test. Since there was a concern about gelatin crosslinking for tafamidis capsules, measures such as strict control of the levels of impurities in the excipients, were taken based on the manufacturing history. However, as the degree of crosslinking was increased in stability studies (at the accelerated storage condition), taking account of the requirements of the USP, the applicant decided to include a second dissolution test using the medium containing digestive enzymes in the specification.

Since there are data suggesting the possibility of altered pharmacokinetics of capsules with extensive crosslinking (higher C_{max}) (Mihara K, et al. *Pharmaceutical Regulatory Science.* 2001;32:804-813), PMDA asked the applicant to explain the appropriateness of determining that capsules with extensive crosslinking

(capsules that do not pass the official dissolution test) conform to the specification, taking also into account that the Japanese Pharmacopoeia does not allow the addition of digestive enzymes to a dissolution medium (Pharmaceutical and Medical Device Regulatory Science Society of Japan, ed. *2011 Japanese Pharmacopoeia Technical Information*).

The applicant explained that the addition of digestive enzymes will be removed from the specification.

PMDA accepted the above and concluded that the drug substance and drug product manufacturing processes, specifications, storage conditions, and shelf-life are appropriate.

2.B.(2) Novel excipient

The drug product contains a novel excipient, sorbitan monooleate.

PMDA concluded as follows:

This excipient meets the requirements of the Japanese Pharmaceutical Excipients (JPE) monograph and there is no particular problem with the specification or stability. In addition, based on the submitted data, the excipient at the level used in the drug product is unlikely to cause a safety problem.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The results from primary pharmacodynamic, secondary pharmacodynamic, and safety pharmacology studies were submitted as pharmacology studies of tafamidis. Since an appropriate animal model of TTR-FAP for drug evaluation is not available, no *in vivo* primary pharmacodynamic studies have been performed. Tafamidis Meglumine or tafamidis (free acid) was used in the studies. All dose levels are expressed as tafamidis.[1)]

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Binding constants of tafamidis to TTR

The binding constants of tafamidis to TTR tetramer were determined using isothermal titration calorimetry.[2)] The dissociation constants for the two binding sites (K_{d1} and K_{d2}) were 3 and 278 nM, respectively (Reference data 4.2.1.1.1).

The binding constants of tafamidis to wild-type TTR tetramer were determined by measuring the rate of labeled TTR subunit exchange.[3)] The K_{d1} and K_{d2} values were 2 and 154 nM, respectively (Reference data 4.2.1.1.2).

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1) (Amount of the meglumine salt of tafamidis) = 1.634 × (Amount of tafamidis)

2) A solution of tafamidis was titrated into a buffer containing wild-type TTR and the heat released during the interaction between tafamidis and TTR tetramer was measured.

3) Homotetramers of wild-type TTR and wild-type TTR labeled at the N terminus with an acidic tag were incubated at an equimolar ratio to initiate subunit exchange between them and the various mixed tetramers of labeled/unlabeled subunits were separated and quantified by anion exchange chromatography over time for kinetic analysis of subunit exchange.

3.(i).A.(1).2) Crystal structure of tafamidis bound to TTR as determined by X-ray diffraction (Reference data 4.2.1.1.3)

The crystal structure of the TTR-tafamidis complex was analyzed by X-ray diffraction, which revealed that the 3,5-chloro groups of tafamidis are placed in the halogen-binding pockets (HBPs) 3 and 3' making hydrophobic interactions, whereas the carboxylate of tafamidis engages in water mediated H-bonds with the Lys15/15' residues of TTR at the periphery of the HBPs 1 and 1' (Figure 1).

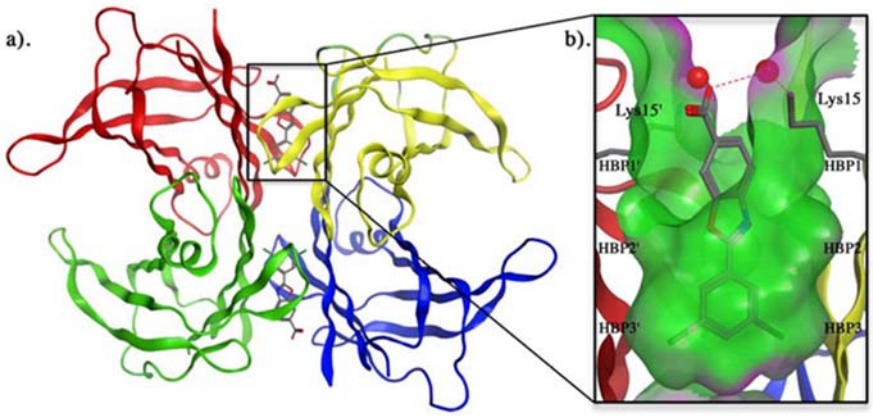

Figure 1. Crystal structure of wild-type TTR-tafamidis complex
(a) Three-dimensional ribbon diagram, b) Magnified image (green, hydrophobic; purple, polar)

3.(i).A.(1).3) Inhibition by tafamidis of TTR tetramer dissociation as measured by subunit exchange under nondenaturing conditions (Reference data 4.2.1.1.2)

The effect of tafamidis (tafamidis:TTR tetramer molar ratios of 0.25-1.5) on the rate of labeled TTR subunit exchange[3)] was assessed. Tafamidis slowed subunit exchange in a concentration-dependent manner. In the presence of tafamidis at a tafamidis:TTR tetramer molar ratio of 0.25, the fraction of exchange was 98.34% after a 96-hour incubation, while at a molar ratio of 1.5, the fraction of exchange was 4.72%.

3.(i).A.(1).4) Binding selectivity of tafamidis to TTR tetramer in human plasma (4.2.1.1.4)

Tafamidis (7.2 μM) was incubated with human plasma containing 3.6 μM[4)] TTR overnight at 37ºC and TTR with bound tafamidis was captured using a resin-bound anti-TTR antibody and the amount of free tafamidis was quantified. The stoichiometry of tafamidis relative to TTR was 0.81 ± 0.02.

3.(i).A.(1).5) Inhibition of TTR fibril formation by tafamidis under acidic denaturing conditions (Reference data 4.2.1.1.5)

A buffer containing wild-type or mutant (V30M or V122I) TTR (3.6 μM[4)]) was added with tafamidis or diflunisal (both 0.9-7.2 μM) and then incubated for 72 hours at 37ºC to assess the inhibition of TTR amyloid fibril formation. The pH was adjusted to 4.4 with acid buffer solution. Tafamidis concentration-dependently inhibited TTR fibril formation, regardless of TTR genotype and the 50% effective concentrations (EC_{50}) for wild-type, V30M, and V122I were 2.7, 3.2, and 4.1 μM, respectively. The EC_{50} values of diflunisal were 2.8, 4.0, and 4.8 μM, respectively.

4) Average TTR concentration in human plasma

3.(i).A.(1).6) Inhibition of TTR tetramer dissociation by tafamidis under urea denaturing conditions (Reference data 4.2.1.1.6)

A solution containing TTR (1.8 μM) and tafamidis (tafamidis:TTR tetramer molar ratios of 1 and 2) was added with urea (5.2 M final concentration) and incubated for 72 hours to assess the inhibition of TTR tetramer dissociation by tafamidis under urea denaturating conditions. As a result, 33% of the TTR tetramer were denatured at a tafamidis:TTR tetramer molar ratio of 1 and <3% of tetramers were denatured at a molar ratio of 2.

3.(i).A.(1).7) Tafamidis Meglumine or tafamidis inhibition of TTR tetramer dissociation in human plasma under urea denaturing conditions (4.2.1.1.7)

Plasma samples from healthy volunteers (TTR concentration, 3.6 μM[4)]) were added with tafamidis (3.6-14.4 μM) and then incubated in the presence of urea (4.8 M) for 4 days and the inhibition of TTR tetramer dissociation by tafamidis was qualitatively analyzed by measuring the remaining amount of TTR tetramer using Western blotting. Nearly complete TTR tetramer dissociation was observed by day 3 of incubation in the absence of tafamidis. In the presence of ≥5.4 μM tafamidis, TTR tetramer remained even after day 3 and even 3.6 μM tafamidis weakly stabilized TTR tetramers. Also in plasma samples with a TTR concentration lower (2.8 μM) or higher (5 μM) than the average concentration, tafamidis (3.6-7.2 μM) inhibited TTR tetramer dissociation in a concentration-dependent manner.

The inhibition of TTR tetramer dissociation by tafamidis or diflunisal (both 7.2 μM) was assessed at an urea concentration of 5.6 M. In the presence of tafamidis, TTR tetramer remained even after day 4 of incubation, while TTR tetramer almost disappeared in the presence of diflunisal.

Using plasma samples from TTR-FAP patients carrying the V30M mutation, the inhibition of TTR tetramer dissociation by Tafamidis Meglumine (7.2 μM) under urea (4.8 M) denaturating conditions was assessed. As a result, the effect of Tafamidis Meglumine was almost equivalent to that in plasma samples from healthy volunteers.

3.(i).A.(1).8) Tafamidis Meglumine inhibition of wild-type and mutant (V30M and V122I) TTR tetramer dissociation in human plasma under urea denaturating conditions as measured by an immunoturbidimetric stabilization assay (4.2.1.1.8)

Human plasma containing wild-type or mutant (V30M or V122I) TTR was added with Tafamidis Meglumine (3.6 or 7.2 μM) and then incubated in the presence of urea (4.8 M) for 2 days and the inhibition of TTR tetramer dissociation by Tafamidis Meglumine was quantitatively analyzed by immunoturbidity. For wild-type TTR, 3.6 and 7.2 μM of Tafamidis Meglumine resulted in the percent stabilization[5)] (mean ± standard deviation

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5) The fraction of initial (FOI) was calculated based on TTR tetramer concentrations before and after incubation, using the following formula and as a quantitative measure of TTR tetramer stabilization, the percent stabilization (%) was calculated based on the FOI for vehicle control (DMSO) and Tafamidis Meglumine, using the following formula.

FOI = [TTR tetramer concentration after incubation]/[initial TTR tetramer concentration]

Percent stabilization = $[(FOI_{\text{Tafamidis Meglumine}} - FOI_{DMSO})/FOI_{DMSO}] \times 100$

[SD]) of 96 ± 42.7% and 181 ± 76.4%, respectively. The percent stabilization was 62 ± 25.9% and 116 ± 35.8%, respectively, for V30M and 237% and 403%, respectively, for V122I.[6)]

3.(i).A.(1).9) Tafamidis Meglumine stabilization of amyloidogenic TTR variants in plasma (4.2.1.1.9)

Using plasma samples from subjects harboring 26 different TTR mutations (n = 27), the inhibition of TTR tetramer dissociation by Tafamidis Meglumine (7.2 μM) was analyzed by immunoturbidity. The results from individual subjects were as shown in Table 3. As TTR tetramer was undetectable after incubation with vehicle control, the percent stabilization could not be calculated for D18E, V30G, F64S, and Y78F. However, TTR tetramer was quantifiable after incubation with Tafamidis Meglumine for F64S and Y78F, suggesting the stabilization effect of Tafamidis Meglumine. D18E- and V30G-TTR were stabilized by Tafamidis Meglumine in a second experiment (percent stabilization, 375% and 700%, respectively). The fraction of initial for vehicle control was low for P24S and Y114C and a second experiment was performed. As a result, the results were reproducible for Y114C, whereas stabilization of P24S-TTR was not observed.

Table 3. Tafamidis Meglumine stabilization of a broad range of TTR variants

TTR mutation	Percent stabilization (%)	TTR mutation	Percent stabilization (%)	TTR mutation	Percent stabilization (%)	TTR mutation	Percent stabilization (%)
C10R	59	K35T	138	E54Q	1050	I84S	159
D18E	n/a	A36P	533	E54K	69	H88R	118
P24S	107	D38A	139	L55Q	333	E89Q	155
A25S	150	W41L	100	F64S	n/a	E89Q	183
V30G	n/a	G47E	126	Y69H	258	A97S	600
R34S	231	T49A	72	V71A	139	Y114C	600
R34T	225	S50R	342	Y78F	n/a		

n/a: Not calculable

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Inhibition of ligand binding or enzyme activity (Reference data 4.2.1.2.1)

The inhibition of ligand binding to 52 receptors/ion channels/transporters and cyclooxygenase (COX)-1 and -2 by tafamidis (10 μM) were assessed. Tafamidis inhibited ligand binding to the δ-opioid receptor by 72%. The inhibition constant of tafamidis for the δ-opioid receptor was 4.9 μM.

3.(i).A.(2).2) δ-opioid receptor bioassay (Reference data 4.2.1.2.2)

In a functional assay using the hamster isolated vas deferens to assess the functional significance of the binding to δ-opioid receptors, tafamidis (3-30 μM) concentration-dependently inhibited the electrically evoked contractions of the hamster vas deferens. A δ-opioid receptor antagonist, naltrindole (0.1 μM) reduced the agonistic activity of tafamidis (30 μM) from 88% to 41%. When tafamidis (3-30 μM) was given in the presence of a δ-opioid receptor agonist, DPDPE ([d-Pen2,d-Pen5]-enkephalin), the agonistic activity of DPDPE was not altered. Thus, tafamidis is considered to have no δ-opioid receptor antagonistic activity.

6) Pooled plasma was used.

3.(i).A.(2).3) Effects on COX activity in human whole blood (4.2.1.2.3)

COX-1 and -2 inhibition by Tafamidis Meglumine (0.1-300 μM) was assessed by the formation of thromboxane B_2 in human whole blood stimulated with A23187 (calcium ionophore, 50 μM). Tafamidis Meglumine had no inhibitory effects on COX-1 and -2.

COX-2 inhibition by Tafamidis Meglumine (0.1-300 μM) was assessed by the formation of prostaglandin E_2 in human whole blood stimulated with A23187 (50 μM). Tafamidis Meglumine had no inhibitory effects on COX-2.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on central nervous system (4.2.1.3.1)

Following the oral administration of Tafamidis Meglumine (10-100 mg/kg) to rats (vehicle, 0.5% methylcellulose [MC]), the effects of Tafamidis Meglumine on the autonomic function, response and sensitivity, excitement, ambulation and sensorimotor coordination, general signs, and body weight were assessed. Body weight loss was observed at ≥30 mg/kg in females and at 100 mg/kg in males.

3.(i).A.(3).2) Effects on cardiovascular and respiratory systems

Using HEK-293 cells stably expressing hERG channels, the effects of Tafamidis Meglumine (1-30 μM) on hERG current were assessed. Tafamidis Meglumine did not inhibit hERG current (4.2.1.3.2).

Following the oral administration of Tafamidis Meglumine (10-300 mg/kg) to conscious dogs (vehicle, 0.5% MC),[7)] the effects of Tafamidis Meglumine on blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure), heart rate, respiratory rate, core body temperature, ECG (PR, QRS, RR, QT, and QTcF intervals), and arterial blood gases (pH, pCO_2, pO_2, SO_2, HCO_3^-) were assessed. Although there were no effects on cardiovascular and respiratory parameters, emesis occurred in 2 of 4 animals at 100 mg/kg and in 4 of 4 animals at 300 mg/kg and salivation was observed in 1 of 4 animals and leg twitching in another animal at 100 and 300 mg/kg (4.2.1.3.3).

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Mechanism of action of tafamidis

PMDA asked the applicant to explain the pathogenesis of TTR-FAP and then explain the mechanism of action of tafamidis.

The applicant explained as follows:

TTR-FAP is characterized by deposition of amyloid composed of a mutant form of TTR in the peripheral and autonomic nervous systems, causing neuropathy (Ando Y, et al. *Rare/Intractable Disease Project supported by the Health and Labour Sciences Research Grants: Amyloidosis Research Committee, 2010 Clinical Practice Guideline for Amyloidosis*, 2010;20-26). TTR is synthesized primarily in the liver and four 127-amino acid

7) Vehicle (0.5% MC) and 10, 100, and 300 mg/kg of Tafamidis Meglumine were administered on Study Days 1, 4, 8, and 11, respectively.

monomers associate to form a tetramer. The process of formation of TTR amyloid fibrils consists of the following steps: (a) TTR tetramers dissociate into monomers, (b) normally folded monomers undergo partial denaturation to produce misfolded monomers, (c) misfolded monomers self-aggregate forming amyloidogenic intermediates, and (d) amyloidogenic intermediates misassemble into soluble oligomers, profilaments, and filaments (Hammarström P, et al. *Proc Natl Acad Sci USA*. 2002;99 Suppl 4:16427-16432, Quintas A, et al. *J Biol Chem*. 2001;276:27207-27213). In this process, TTR tetramer dissociation as defined in the step (a) is considered the rate-limiting step in the formation of amyloid fibrils (Colon W, et al. *Biochemistry*. 1992;31:8654-8660). In patients with TTR-FAP, ≥60 variants of TTR have been reported (Connors LH, et al. *Amyloid*. 2003;10:160-184) and not all of these variants have been studied for the mechanism of formation of TTR amyloid fibrils, but the stability of wild-type and mutant TTR tetramers (L55P-TTR [the variant associated with the most aggressive form of amyloidosis], V30M-TTR [one of the most common amyloidogenic TTR variants in TTR-FAP patients], T119M-TTR [a non-amyloidogenic variant of TTR]) was determined, which suggested decreased stability of the L55P- and V30M-TTR tetramers (Quintas A, et al. *J Biol Chem*. 2001;276:27207-27213). Thus, in TTR-FAP patients, amyloid fibril formation is promoted by unstable TTR tetramers, regardless of the TTR mutation.

It was found that tafamidis binds to the two thyroxine binding sites of the TTR tetramer (Reference data 4.2.1.1.1-4.2.1.1.3), that tafamidis inhibited TTR tetramer dissociation under non-denaturing and urea denaturing conditions (Reference data 4.2.1.1.2, Reference data 4.2.1.1.6, 4.2.1.1.7), and that tafamidis inhibited TTR amyloid fibril formation under acidic denaturing conditions (Reference data 4.2.1.1.5). Since tafamidis inhibited tetramer dissociation in human plasma for almost all of the TTR variants tested (4.2.1.1.8, 4.2.1.1.9), tafamidis is considered to inhibit TTR tetramer dissociation, regardless of the TTR mutation in TTR-FAP patients.

PMDA asked the applicant to discuss the influence of different TTR mutations on the effects of tafamidis from a pharmacological point of view.

The applicant explained as follows:
At least 100 variants of TTR (including non-amyloidogenic variants) have been reported and ≥60 of them are considered associated with TTR-FAP. In a study that assessed the ability of tafamidis to stabilize 26 different TTR variants (4.2.1.1.9), tafamidis demonstrated stabilization of 25 of the 26 TTR variants tested, but stabilization of P24S-TTR was not observed. This result was inferred to be associated with the use of plasma samples stored for a long period of time. Thus, regardless of the TTR mutation, tafamidis is expected to stabilize TTR. It has been reported that there are TTR variants (A25T, D18G) that are predominantly associated with CNS deposition and lead to milder systemic neuropathy and/or cardiomyopathy in spite of being more destabilized than L55P (the most pathogenic systemic variant). The finding is considered due to highly destabilized TTR variants being subjected to endoplasmic reticulum-associated degradation in their producing cells, resulting in reduced efficiency of secretion into the blood (Sekijima Y, et al. *Cell*. 2005;121:73-85). Since the protein binding of tafamidis in human peripheral blood is >99.5% (4.2.2.3.4) and intracellular distribution

of tafamidis is considered limited, it is unlikely that administration of tafamidis improves the reduced efficiency of secretion into the blood, resulting in increases in the plasma TTR tetramer concentration and the effects of tafamidis are unlikely to differ significantly in patients with these mutations.

Based on the above, is the applicant considered that the binding of tafamidis to the TTR tetramer prevents the dissociation of the TTR tetramer into monomers (which is the rate-limiting step in TTR amyloidogenesis) and thereby inhibits TTR amyloid fibril formation to delay peripheral neurologic impairment in patients with TTR-FAP.

PMDA considers that the applicant's explanation is acceptable, but that it is necessary to draw a conclusion on the efficacy of tafamidis in humans, taking account of clinical study data.

3.(i).B.(2) Safety of tafamidis

PMDA asked the applicant to explain whether or not the findings observed in safety pharmacology studies are of clinical relevance.

The applicant explained as follows:

In a rat study (4.2.1.3.1), body weight loss was observed at ≥30 mg/kg in females and at 100 mg/kg in males. In a 28-day repeated oral dose toxicity study in rats, reduced body weight associated with reduced food consumption was observed at ≥100 mg/kg/day. These findings are considered attributable to decreased appetite caused by the precipitation and accumulation of tafamidis in the acidic gastric environment. In a dog study (4.2.1.3.3), emesis, salivation, and leg twitching were observed at ≥100 mg/kg. It is considered that emesis and salivation were caused by irritation of the stomach by drug precipitation. Although the mechanism of development of leg twitching is unknown, this finding is considered to be part of non-specific toxic changes associated with high-dose administration, as the C_{max} in dogs following oral administration of 100 mg/kg of tafamidis (135 μg/mL [4.2.1.3.3]) was approximately 52-fold the C_{max} (2.61 μg/mL[8)]) at the clinical human dose. Emesis observed in dogs may have been related to the agonistic activity of tafamidis at δ-opioid receptors (Reference data 4.2.1.2.1, Reference data 4.2.1.2.2). However, the EC_{50} of tafamidis is ≥10 μM while the C_{max} at the clinical human dose is 8.5 μM[8)] and the human plasma protein binding of tafamidis is >99.5% (4.2.2.3.4). Taking account of these findings, adverse events mediated by the δ-opioid receptor activation are unlikely to be of clinical relevance. When the C_{max} (rat, 32.3 μg/mL[9)]; dog, 34.0 μg/mL [4.2.1.3.3]) and $AUC_{0\text{-last}}$ (rat, 536 μg·h/mL[9)]; dog, 483 μg·h/mL[10)]) at the no-observed-effect-levels (rat, 10 mg/kg; dog, 10 mg/kg) in *in vivo* safety pharmacology studies were compared with the C_{max} and $AUC_{0\text{-last}}$[8)] at the clinical human dose, the safety margins were 12- to 13-fold based on the C_{max} values and 9.1- to 10-fold based on the $AUC_{0\text{-last}}$ values. On the basis of the above, the findings observed in the safety pharmacology studies are unlikely to be of clinical

[8)] Estimates at steady state following once daily administration of Tafamidis Meglumine 20 mg to Japanese patients, based on a population pharmacokinetic analysis of Japanese and foreign subjects (5.3.3.5.1) (C_{max}, 2.61 μg/mL [8.5 μM]; $AUC_{0\text{-last}}$, 53.3 μg·h/mL)[9)] Data on Day 1 in a 28-day repeated oral dose toxicity study in rats (4.2.3.2.3)

[9)] Data on Day 1 in a 28-day repeated oral dose toxicity study in rats (4.2.3.2.3)

[10)] Data from females on Day 1 in a 28-day repeated oral dose toxicity study in dogs (4.2.3.2.5)

relevance.

Tafamidis binding to the TTR tetramer leads to the inhibition of TTR function. PMDA asked the applicant to explain whether or not any safety issues may arise from the inhibition of TTR function.

The applicant explained as follows:
TTR is known to transport thyroxine or create a pool of thyroxine and transport vitamin A, and it has also been reported that TTR promotes insulin release (Refai E, et al. *Proc Natl Acad Sci USA*. 2005;102:17020-17025). Although the effects of tafamidis on these functions have not been studied, no adverse events related to thyroid function[11] occurred in a Japanese phase III study (5.3.5.2.3, Study B3461010) and the incidences of adverse events related to thyroid function were 1.6% (1 of 63 subjects) in the placebo group and 0% (0 of 65 subjects) in the tafamidis group in a foreign phase II/III study (5.3.5.1.1, Study Fx-005) and only 1.2% (1 of 85 subjects) in the tafamidis group in a foreign long-term extension study (5.3.5.2.1, Study Fx-006). In humans, 75% of the circulating thyroxine is bound to thyroid binding globulin and 10% is bound to albumin (Suzuki S. *Shinshu Medical Journal.* 2011;59:403-410) and the effects of the inhibition of TTR function are considered limited. Concerning the effects associated with changes in the biokinetics of vitamin A, although ophthalmic findings (e.g., small eyes) were observed in an embryo-fetal development oral study in rabbits (4.2.3.5.2.4), these findings were accompanied by small eye sockets and may have been secondary to skeletal variations. In addition, adverse events related to vitamin A deficiency[12] occurred in only 1 of 10 subjects in Study B3461010 (5.3.5.2.3), and the incidences of adverse events related to vitamin A deficiency were 14.3% (9 of 63 subjects) in the placebo group and 12.3% (8 of 65 subjects) in the tafamidis group, showing no trend towards a higher incidence in the tafamidis group than in the placebo group in Study Fx-005 (5.3.5.1.1). No adverse events related to increases in blood glucose[13] were reported in Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010). Based on the above, the inhibition of TTR function by tafamidis is unlikely to cause clinically relevant events.

PMDA considers that the applicant's explanation is acceptable, but that it is necessary to continue to collect information on the occurrence of adverse events related to the inhibition of TTR function (adverse events related to thyroid function, vitamin A deficiency, and increases in blood glucose) via post-marketing surveillance because there is limited clinical experience with tafamidis.

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11) Events in the MedDRA SMQs "hyperthyroidism" and "hypothyroidism", HLTs "thyroid analyses", "thyroid histopathology procedures", "parathyroid analyses", and "parathyroid histopathology procedures," and PTs: blood thyroid stimulating hormone abnormal; blood thyroid stimulating hormone decreased; blood thyroid stimulating hormone increased; blood thyroid stimulating hormone; thyroid releasing hormone challenge test abnormal; and thyroid releasing hormone challenge test.

12) Events in the MedDRA SMQ "lacrimal disorders" and PTs: dry eye; lacrimation decreased; lacrimal disorder; keratomalacia; xerophthalmia; vitamin A deficiency; vitamin A deficiency related corneal disorder; vitamin A deficiency eye disorder; vitamin A deficiency related conjunctival disorder; night blindness; corneal deposits; corneal leukoma; corneal lesion; corneal degeneration; and dry skin.

13) Events in the MedDRA SMQ "hyperglycaemia/new onset diabetes mellitus", HLGT "diabetic complications", and HLTs "hyperglycaemic conditions NEC", "diabetes mellitus (incl subtypes)", and "carbohydrate tolerance analyses (incl diabetes)" (excluding "decreased" PTs under the HLT "carbohydrate tolerance analyses (incl diabetes)").

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The results from absorption, distribution, metabolism, and excretion studies in mice, rats, rabbits, and dogs were submitted. Plasma tafamidis concentrations were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 10-100 ng/mL). In studies using ^{14}C-Tafamidis Meglumine, radioactivity in biomaterials and excreta was measured by liquid scintillation counter (LSC) (detection limit, two times the background radioactivity). Unless otherwise specified, dose levels are expressed as tafamidis (free acid)[1)] and the time to maximum plasma concentration (t_{max}) is expressed as the median and other pharmacokinetic parameters are expressed as the mean or the mean ± SD.

3.(ii).A.(1) Absorption

Following a single oral administration of 20, 60, or 200 mg/kg of Tafamidis Meglumine (vehicle, 7.5% aqueous solution of vitamin E *d*-α-tocopherol-polyethylene glycol 1000 succinate [VE TPGS]) to male mice (n = 5/timepoint/group) under fasted conditions, the pharmacokinetic parameters of tafamidis in plasma were as shown in Table 4 (4.2.2.2.1).

Table 4. Pharmacokinetic parameters of tafamidis in plasma following a single oral administration of Tafamidis Meglumine to male mice

Dose (mg/kg)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
20	39.8	0.5	7.1	263
60	52.9	8	-	816
200	161	1	-	1730

n = 5/timepoint/group
-: Not calculated

Following a single oral administration of 3, 10, or 30 mg/kg of Tafamidis Meglumine (vehicle, 7.5% VE TPGS) to male rats (n = 2/group) under fasted conditions, tafamidis in plasma was still quantifiable at 168 hours post-dose (the last sampling point) and the C_{max} values were 9.06, 35.3, and 102 μg/mL, respectively, and the $AUC_{0\text{-}\infty}$ values were 216, 512, and 2590 μg·h/mL, respectively (4.2.2.2.3).

Following a single oral administration of 20 mg/kg of tafamidis (vehicle, 0.5% MC) to male rats (n = 3) under fasted conditions, tafamidis reached a C_{max} in plasma (101 ± 7.55 μg/mL) at 2 hours post-dose and the $AUC_{0\text{-}8h}$ was 618 ± 28.1 μg·h/mL. The terminal phase could not be characterized within the sampling period (8 hours) and the elimination half-life ($t_{1/2}$) could not be calculated (4.2.2.2.2).

Following a single oral administration of 1 mg/kg of tafamidis (vehicle, 0.5% MC) to male rats (n = 3) under fasted conditions, tafamidis reached a C_{max} in plasma (3.57 ± 0.718 μg/mL) at 4 hours post-dose and was eliminated with a $t_{1/2}$ of 11.6 ± 4.47 hours. The $AUC_{0\text{-}\infty}$ was 69.1 ± 10.6 μg·h/mL (4.2.2.2.2).

Following a single oral administration of 1.8 mg/kg of Tafamidis Meglumine (vehicle, 0.5% MC) to male rats (n = 3) under fasted conditions, tafamidis reached a C_{max} in plasma (7.32 ± 1.33 μg/mL) at 4 hours post-dose and was eliminated with a $t_{1/2}$ of 13.6 ± 3.07 hours. The $AUC_{0\text{-}\infty}$ was 126 ± 39.8 μg·h/mL (4.2.2.2.3).

Following a single oral administration of 10 or 100 mg/kg of Tafamidis Meglumine (vehicle, 0.5% MC or 7.5% VE TPGS) to male rats (n = 2/group) under fasted conditions, the plasma $AUC_{0\text{-}24h}$ values of tafamidis were 344 and 445 µg·h/mL, respectively, at 10 mg/kg and 2070 and 2910 µg·h/mL, respectively, at 100 mg/kg and the $AUC_{0\text{-}24h}$ values were 29% to 41% higher when 7.5% VE TPGS was used as vehicle (4.2.2.2.3).

Following a single oral administration of 10, 30, or 100 mg/kg of Tafamidis Meglumine (vehicle, 7.5% VE TPGS) to male rats (n = 3/timepoint/group) under non-fasting conditions, the plasma C_{max} values of tafamidis were 34.2, 82.6, and 177 µg/mL, respectively, and the $AUC_{0\text{-}24h}$ values were 447, 1380, and 3450 µg·h/mL, respectively. The t_{max} tended to be prolonged at 100 mg/kg compared to lower doses (1, 2, and 12 hours at 10, 30, and 100 mg/kg, respectively) (4.2.3.7.7.1).

Following a single oral administration of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 µCi/animal) (vehicle, 7.5% VE TPGS) to male and female rats (n = 3-5/sex/timepoint) under non-fasting conditions, the pharmacokinetic parameters of radioactivity in plasma and whole blood were as shown in Table 5 and these parameters were similar between males and females (4.2.2.2.4).

Table 5. Pharmacokinetic parameters of radioactivity in plasma and whole blood following a single oral administration of ^{14}C-Tafamidis Meglumine to male and female rats

		C_{max} (µg eq./mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}\infty}$ (µg eq.·h/mL)
Plasma	Male	11.3	2	43.1	368
	Female	11.6	1	40.9	394
Whole blood	Male	6.75	2	41.7	224
	Female	6.98	1	41.3	236

n = 3/sex/timepoint (n = 5/sex/timepoint at 168 hours only)

Following a single oral administration of 1 mg/kg of tafamidis (vehicle, 0.5% MC) to male rats (n = 2) under non-fasting conditions, tafamidis reached a C_{max} in plasma (1.61 µg/mL) at 2 hours post-dose in one rat or at 4 hours post-dose in the other rat and the $t_{1/2}$ and $AUC_{0\text{-}24h}$ were 30.6 hours and 28.5 µg·h/mL, respectively (4.2.2.2.2).

Following a single intravenous administration of 2 mg/kg of tafamidis to male rats (n = 3), the $t_{1/2}$, volume of distribution (V_z), clearance, and $AUC_{0\text{-}\infty}$ of tafamidis in plasma were 9.2 ± 1.2 hours, 316 ± 35.7 mL/kg, 24.0 ± 3.46 mL/kg/h, and 84.4 ± 11.6 µg·h/mL, respectively. Following a single oral administration of 2 mg/kg of tafamidis (vehicle, 0.5% MC) to male rats (n = 3) under fasted conditions, the absolute bioavailability (BA) of oral versus intravenous tafamidis was 108% (4.2.2.2.2).

Following a single oral administration of 30, 60, or 80 mg/kg of Tafamidis Meglumine (vehicle, 7.5% VE TPGS) to male dogs (n = 2/group) under fasted conditions, the plasma C_{max} values of tafamidis were 87.6, 130, and 160 µg/mL, respectively, the $AUC_{0\text{-}\infty}$ values were 1455, 2260, and 3390 µg·h/mL, respectively, and the increases in the C_{max} were less than dose-proportional (4.2.2.2.3).

Following a single oral administration of 5 mg/kg of tafamidis (vehicle, 0.5% carboxymethylcellulose) to male

dogs (n = 3) under fasted conditions, tafamidis reached a C_{max} in plasma (17.5 ± 2.10 μg/mL) at 1 hour post-dose and the $t_{1/2}$, AUC_{0-24h}, and $AUC_{0-\infty}$ were 12.5 hours,[14)] 233 ± 24.2 μg·h/mL, and 335 μg·h/mL,[14)] respectively (4.2.2.2.2).

Following a single oral administration of 1 mg/kg of tafamidis (vehicle, 0.5% MC) to male dogs (n = 3) under fasted conditions, tafamidis reached a C_{max} in plasma (4.96 ± 1.26 μg/mL) at 2 hours post-dose and the $t_{1/2}$, AUC_{0-24h}, and $AUC_{0-\infty}$ were 20.5 ± 6.2 hours, 68.2 ± 11.2 μg·h/mL, and 120 ± 33.6 μg·h/mL, respectively (4.2.2.2.2).

Following a single oral administration of 1.5 to 100 mg/kg of Tafamidis Meglumine in a 0.5% MC suspension, a 7.5% VE TPGS solution, a size 00 hydroxypropylmethylcellulose (HPMC) capsule, or a size 2 HPMC capsule to male dogs (n = 2/group) under fasted conditions, the C_{max} and AUC_{0-24h} were 17% to 28% (10 mg/kg) or 87% to 112% (100 mg/kg) higher after administration of the drug in a 7.5% VE TPGS solution compared to a 0.5% MC suspension and 75% to 81% (10 mg/kg) or 48% to 56% (100 mg/kg) lower after administration of the drug in a capsule compared to a 0.5% MC suspension (4.2.2.2.3).

Following a single oral administration of 1.4 to 5.1 mg/kg (as the meglumine salt) of Tafamidis Meglumine in a 7.5% VE TPGS solution (2 mg/kg), a hard capsule (2.9 mg/kg), or a soft capsule (1.4 or 5.1 mg/kg) to male dogs (n = 3/group) under fasted conditions, the C_{max} per dose and the $AUC_{0-\infty}$ per dose were 22% to 23% lower after administration of the drug in a hard capsule, 22% to 29% higher after administration of the drug in a soft capsule (1.4 mg/kg), and 28% to 48% lower after administration of the drug in a soft capsule (5.1 mg/kg), compared to the drug in a 7.5% VE TPGS solution (4.2.2.2.3).

Following a single oral administration of 1.5 mg/kg (as the meglumine salt) of Tafamidis Meglumine (dosage form, soft capsule) to male dogs (n = 3/group) under fasted conditions, tafamidis reached a C_{max} in plasma (3.66 ± 0.042 μg/mL) at 2 hours post-dose and the $t_{1/2}$ and $AUC_{0-\infty}$ were 19.6 ± 2.32 hours and 72.8 ± 20.6 μg·h/mL, respectively (4.2.2.2.3).

Following a single intravenous administration of 1 mg/kg of Tafamidis Meglumine to male dogs (n = 3), the $t_{1/2}$, V_z, and $AUC_{0-\infty}$ of tafamidis in plasma were 9.6 hours,[15)] 317 mL/kg,[15)] and 43.8 μg·h/mL,[15)] respectively. Following a single oral administration of 1 mg/kg of Tafamidis Meglumine (vehicle, 0.5% MC) to male dogs (n = 3) under fasted conditions, the absolute BA[16)] of oral versus intravenous tafamidis was 91% (4.2.2.2.2).

Male and female mice (n = 3/sex/timepoint/group) were orally administered 10, 30, 60, 120, or 240[17)] mg/kg/day of Tafamidis Meglumine once daily for 25 days (10, 30, 60 mg/kg/day) or 28 days (120 and 240 mg/kg/day) (vehicle, 7.5% VE TPGS). The pharmacokinetic parameters of tafamidis in plasma after the last

14) Since the values represent the mean of 2 animals, SD has not been calculated.

15) Since the parameters are calculable for 1 animal only, SD has not been calculated.

16) Since the percentage of $AUC_{0-\infty}$ extrapolated (after oral administration) is high (44.9%), BA has been calculated based on AUC_{0-24h}.

17) Since males were sacrificed early due to toxicity, the pharmacokinetics of 240 mg/kg/day were determined in females only.

dose were similar between male and female mice and the C_{max} tended to be less than dose-proportional at ≥120 mg/kg/day (4.2.3.2.1).

Male and female mice (n = 3/sex/timepoint/group) were orally administered 10, 30, or 90 mg/kg/day of Tafamidis Meglumine once daily for 26 weeks (vehicle, 7.5% VE TPGS). The pharmacokinetic parameters of tafamidis in plasma on Days 1 and 93 were as shown in Table 6 and no major gender differences were observed (4.2.3.4.2.1).

Table 6. Pharmacokinetic parameters of tafamidis in plasma
after 26-week oral administration of Tafamidis Meglumine to male and female mice

Dose (mg/kg/day)	Timepoint	C_{max} (μg/mL)		t_{max} (h)		$t_{1/2}$ (h)		AUC_{0-24h} (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
10	Day 1	14.4	11.8	1.0	0.5	8.48	8.12	125	108
	Day 93	21.1	17.4	1.0	0.5	-	10.0	193	178
30	Day 1	39.9	37.6	0.5	0.5	6.34	8.32	418	337
	Day 93	85.5	57.3	0.5	0.5	9.50	7.60	625	474
90	Day 1	74.9	83.9	0.5	0.5	11.1	10.7	1131	1080
	Day 93	101	92.8	0.5	1.0	-	9.58	1635	1564

n = 3/sex/timepoint/group

Male rats (n = 3) were orally administered 1 mg/kg/day of Tafamidis Meglumine once daily for 5 days (vehicle, 0.5% MC). The plasma C_{max} values of tafamidis on Days 1 and 5 were 2.05 ± 0.230 and 3.90 ± 0.793 μg/mL, respectively, and the AUC_{0-24h} values were 32.3 ± 2.46 and 60.3 ± 10.9 μg·h/mL, respectively (4.2.2.2.2).

Female rats (n = 5/group) were orally administered 10, 30, or 100 mg/kg/day of tafamidis once daily for 10 days (vehicle, 0.5% MC). The plasma tafamidis concentrations at 24 hours post-dose on Day 10 were 43.9 ± 9.99, 96.5 ± 15.5, and 161 ± 28.8 μg/mL, respectively (Reference data 4.2.3.2.2).

Male and female rats (n = 3/sex/timepoint/group) were orally administered 10, 30, or 100 mg/kg/day of Tafamidis Meglumine once daily for 28 days (vehicle, 0.5% MC). The plasma C_{max} and AUC_{0-24h} values of tafamidis on Day 28 (male/female) were as shown in Table 7 (4.2.3.2.3).

Table 7. Plasma C_{max} and AUC_{0-24h} values of tafamidis
after 28-day oral administration of Tafamidis Meglumine to male and female rats

	10 mg/kg/day		30 mg/kg/day		100 mg/kg/day	
	Male	Female	Male	Female	Male	Female
C_{max} (μg/mL)	73.3	63.3	124	136	222	240
AUC_{0-24h} (μg·h/mL)	1010	1170	1980	2480	4190	4220

n = 3/sex/timepoint/group

Male and female rats (n = 3/sex/timepoint/group) were orally administered 3, 10, or 30 mg/kg/day of Tafamidis Meglumine once daily for 26 weeks (vehicle, 7.5% VE TPGS). The pharmacokinetic parameters of tafamidis in plasma on Days 1 and 178 were as shown in Table 8 and the C_{max} and AUC_{0-24h} tended to be higher on Day 178 compared to Day 1 (4.2.3.2.4).

Table 8. Pharmacokinetic parameters of tafamidis in plasma
after 26-week oral administration of Tafamidis Meglumine to male and female rats

Dose (mg/kg/day)	Timepoint	C_{max} (μg/mL)		t_{max} (h)		$t_{1/2}$ (h)		$AUC_{0\text{-}24h}$ (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
3	Day 1	8.99	9.98	1	2	14.2	16.8	125	148
	Day 178	25.8	23.3	1	2	19.8	34.7	357	380
10	Day 1	33.2	42.0	2	2	15.1	18.2	451	618
	Day 178	70.1	87.7	1	1	23.7	19.9	1090	1310
30	Day 1	80.4	99.2	4	2	17.2	16.6	1320	1670
	Day 178	137	181	1	8	24.1	-	2260	3120

n = 3/sex/timepoint/group, -: Not calculated

Pregnant rats (n = 3/timepoint/group) were orally administered 15, 30, or 45 mg/kg/day of Tafamidis Meglumine once daily from gestation day 7 to gestation day 17 (vehicle, 7.5% VE TPGS). The pharmacokinetic parameters of tafamidis in plasma on Days 1 and 11 (gestation days 7 and 17) were as shown in Table 9 (4.2.3.5.2.2).

Table 9. Pharmacokinetic parameters of tafamidis in plasma
after 11-day oral administration of Tafamidis Meglumine to pregnant rats

Dose (mg/kg/day)	Timepoint	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
15	Day 1	44.8	0.5	13.3	757
	Day 11	72.8	2	12.6	1090
30	Day 1	83.4	4	-	1270
	Day 11	92.7	4	-	1610
45	Day 1	98.6	4	-	1990
	Day 11	133	4	-	2160

n = 3/timepoint/group, -: not calculated

Pregnant rabbits (n = 3/group) were orally administered 0.5, 2, or 8 mg/kg/day of Tafamidis Meglumine once daily from gestation day 7 to gestation day 19 (vehicle, 7.5% VE TPGS). The pharmacokinetic parameters of tafamidis in plasma on Days 1 and 13 (gestation days 7 and 19) were as shown in Table 10 (4.2.3.5.2.4).

Table 10. Pharmacokinetic parameters of tafamidis in plasma
after 13-day oral administration of Tafamidis Meglumine to pregnant rabbits

Dose (mg/kg/day)	Timepoint	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
0.5	Day 1	3.61 ± 0.0987	4	-	74.9 ± 5.52
	Day 13	8.14 ± 0.650	4	39.1[a)]	157 ± 23.2
2	Day 1	10.3 ± 1.59	4	-	206 ± 48.7
	Day 13	18.5 ± 4.25	4	-	357 ± 119
8	Day 1	41.8 ± 10.3	8	16.1[a)]	795 ± 237
	Day 13	82.9 ± 41.7	2	28.7[b)]	1540 ± 874

n = 3/group, -: Not calculated
a) n = 1 b) n = 2

Male and female dogs (n = 2/sex) were orally administered 45 mg/kg/day of Tafamidis Meglumine once daily for 7 days (vehicle, 7.5% VE TPGS). Tafamidis reached a C_{max} in plasma (142/157 μg/mL) (male/female) at 1.5/2 hours post-dose on Day 7 and the $t_{1/2}$ and $AUC_{0\text{-}24h}$ were 11.2/10.8 hours and 1600/1800 μg·h/mL, respectively. No major gender differences in the C_{max} or $AUC_{0\text{-}24h}$ and no accumulation were observed (4.2.2.2.3).

Male and female dogs (n = 2/sex/group) were orally administered 100 or 300 mg/kg/day of tafamidis once daily for 7 days (vehicle, 0.5% MC). The C_{max} and $AUC_{0\text{-}24h}$ at 300 mg/kg/day were 106% to 110% of those at 100 mg/kg/day, indicating the possibility of saturation of absorption at 100 to 300 mg/kg/day (Reference data 4.2.3.1.1).

Male and female dogs (n = 3 or 5/sex/group) were orally administered 10, 100, or 300/200[18] mg/kg/day of Tafamidis Meglumine once daily for 28 days (vehicle, 0.5% MC). The pharmacokinetic parameters of tafamidis in plasma on Days 1 and 28 were as shown in Table 11 and no major gender differences and no accumulation were observed and there tended to be no further increases in the C_{max} and $AUC_{0\text{-}24h}$ at ≥200 mg/kg/day (4.2.3.2.5).

Table 11. Pharmacokinetic parameters of tafamidis in plasma after 28-day oral administration of Tafamidis Meglumine to male and female dogs

Dose (mg/kg/day)	Timepoint	C_{max} (μg/mL)		t_{max} (h)		$t_{1/2}$ (h)		$AUC_{0\text{-}24h}$ (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
10	Day 1	32.8 ± 7.33	41.1 ± 5.73	2	2	7.0 ± 1.6	10.1 ± 2.25	282 ± 75.7	483 ± 123
	Day 28	33.5 ± 6.98	41.7 ± 0.265	1	1	12.4[b]	8.9 ± 1.2	327 ± 129	435 ± 30.0
100	Day 1	189 ± 14.7	178 ± 19.7	4	4	-	-	2340 ± 267	2190 ± 349
	Day 28	148[c]	160 ± 41.9	1[c]	2	8.6[c]	9.8[b]	1380[c]	1890 ± 479
300/200[a]	Day 1	176 ± 25.8	224 ± 34.2	4	4	-	11.0[b]	2820 ± 736	3230 ± 352
	Day 28	169 ± 31.0[d]	234 ± 44.1[e]	2[d]	2[e]	61.9[b]	11.4 ± 0.624[d]	2980 ± 491[d]	2780 ± 683[e]

n = 3/sex/group for 10 and 100 mg/kg, n = 5/sex/group for 300/200 mg/kg, -: Not calculated
a) The dose was reduced from 300 to 200 mg/kg/day on Day 8 for females and on Day 9 for males.
b) n = 2 c) n = 1 d) n = 3 e) n = 4

Male and female dogs (n = 3 or 5/sex/group) were orally administered 5, 15, or 45 mg/kg/day of Tafamidis Meglumine once daily for 39 weeks (vehicle; 7.5% VE TPGS was initially used, which was changed to 0.5% MC on Day 48). The plasma C_{max} values of tafamidis on Day 271 (male/female) were 29.2 ± 1.51/30.2,[14] 51.1 ± 11.0/57.4 ± 16.6, and 124 ± 19.1/126 ± 19.0 μg/mL, respectively, and the $AUC_{0\text{-}24h}$ values were 331 ± 73.5/444[14], 567 ± 126/699 ± 253, and 1440 ± 287/1810 ± 630 μg·h/mL, respectively (4.2.3.2.6).

3.(ii).A.(2) Distribution

Following a single oral dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 μCi/animal) (vehicle, 7.5% VE TPGS) to male and female albino rats, radioactivity levels peaked within 2 hours post-dose in the majority of tissues and then declined gradually, but radioactivity was still present at 168 hours post-dose. The organ/plasma ratio was >1 at 0.5 hours post-dose for the liver and stomach and at ≥1 hour post-dose for the harderian glands (at all time points after 6 hours post-dose), liver (at all timepoints), and perirenal fat and skin (at 168 hours post-dose). The blood/plasma ratio of radioactivity was approximately 0.6 at all timepoints in both males and females, suggesting limited distribution of tafamidis into blood cells (4.2.2.2.4).

Pregnant albino rats were orally administered 15 mg/kg/day of Tafamidis Meglumine (gestation days 15 and 19, ^{14}C-Tafamidis Meglumine, 10 μCi/animal; other days, unlabeled Tafamidis Meglumine) once daily from gestation day 7 to gestation day 19 (vehicle, 7.5% VE TPGS). Widespread tissue distribution of radioactivity was observed in the dams and fetuses at 1 hour post-dose on gestation days 15 and 19, indicating that tafamidis-derived materials cross the placental barrier. In the fetuses, the highest radioactivity level was detected in the liver, which was higher than the radioactivity level in the fetal blood. The fetal radioactivity level was higher on gestation day 19 compared to gestation day 15 (4.2.2.3.6).

[18] Tafamidis Meglumine was initiated at 300 mg/kg/day, but the dose was reduced to 200 mg/kg/day due to toxicity on Day 8 for females and on Day 9 for males.

When mouse plasma was added with 10 μM of Tafamidis Meglumine, the percentage of plasma protein-bound tafamidis was 97.1% (4.2.2.3.2).

When rat and dog plasma were added with 10 μM of Tafamidis Meglumine, the percentage of plasma protein-bound tafamidis was 99.0% and 99.1%, respectively (4.2.2.3.3).

3.(ii).A.(3) Metabolism

Following a single oral dose of 60 mg/kg of Tafamidis Meglumine to male and female mice, the major component in plasma at 24 hours post-dose was tafamidis and a monoglucuronide (acylglucuronide) metabolite and a trace amount of a monoxide metabolite were detected (4.2.2.4.1).

Following a single oral dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 μCi/animal) or 26-week oral administration of 30 mg/kg/day of Tafamidis Meglumine to male and female rats, the major component in plasma at 1 to 48 hours post-dose was tafamidis and an acylglucuronide metabolite was detected (4.2.2.2.4, 4.2.2.4.2).

Following a single dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine to bile duct cannulated male and female rats, in the bile up to 48 hours post-dose, the major radiolabeled compound was the acylglucuronide (males, 64.1%-68.3%; females, 72.7%-82.3%) and a diastereomer of the acylglucuronide (males, 18.4%-32.0%; females, 17.7%-21.4%) and metabolites M1, M4, M6, M7, and M8 were detected. Tafamidis was not practically detected (males, a trace amount to 1.5%; females, undetectable to 1.8%) (4.2.2.2.4).

Pregnant rabbits were orally administered 0.5 to 8.0 mg/kg/day of Tafamidis Meglumine for 14 days. The major component in plasma at 24 hours post-dose was tafamidis and a monoxide metabolite was detected (4.2.2.4.3).

Male and female dogs were orally administered 45 mg/kg/day of Tafamidis Meglumine for 39 weeks. The major component in plasma at 1 to 24 hours post-dose was tafamidis and an acylglucuronide metabolite and a trace amount of a sulfate conjugate metabolite were detected (4.2.2.4.4).

Based on the above, the proposed metabolic pathways of tafamidis are as shown in Figure 2. The site of oxidation to form the monoxide or the metabolic enzyme responsible for the formation of the monoxide has not been identified.

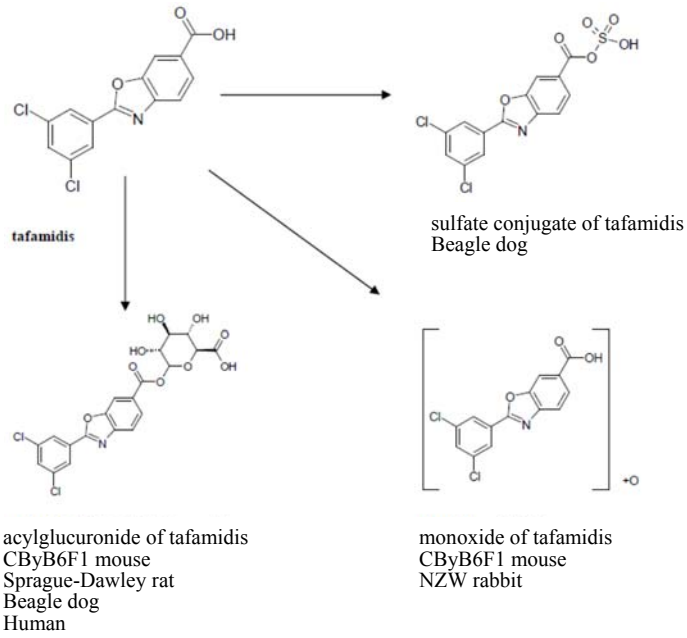

Figure 2. Proposed metabolic pathways of tafamidis

When rat, dog, and monkey liver microsomes or liver S9 fractions were added with 1 μM of tafamidis in the presence of nicotinamide adenine dinucleotide phosphate (NADP), glucose-6-phosphate (G6P), and glucose-6-phosphatase (G6PDHase), ≥96% of tafamidis remained unchanged, indicating that tafamidis is not metabolized by CYP450 (4.2.2.4.8, Reference data 4.2.1.2.1).

When rat and dog liver S9 fractions were added with 1 μM of tafamidis in the presence of NADP, G6P, G6PDHase, glutathione (GSH), and uridine diphosphate glucuronic acid (UDPGA), metabolism of tafamidis was not observed (4.2.2.4.9).

Mouse, rat, rabbit, and dog liver microsomal fractions were added with 10 μM of Tafamidis Meglumine in the presence of NADP, G6P, G6PDHase, GSH, UDPGA, alamethicin (a peptide that forms pores in cell membranes), and saccharolactone (a β-glucuronidase inhibitor), ≥93% of tafamidis remained unchanged across all species while an acylglucuronide metabolite and a monoxide metabolite were detected in mouse microsomal incubation mixture and an acylglucuronide metabolite was detected in rat and dog microsomal incubation mixture. No metabolites were detected in rabbit microsomal incubation mixture (4.2.2.4.10).

3.(ii).A.(4) Excretion

Following a single dose of 3 mg/kg of Tafamidis Meglumine to male rats, urinary tafamidis concentrations for each 24-hour period were measured up to 120 hours post-dose and the highest concentration was observed in the 0- to 24-hour period. Tafamidis was still quantifiable in the 96- to 120-hour period in 2 of 5 rats (4.2.2.2.3).

Following a single oral dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 μCi/animal) to male and female rats, 7.1% to 19% of the administered radioactivity was excreted in the urine and 67% to 79% of the administered radioactivity was excreted in the feces by 168 hours post-dose. In the urine up to 72 hours post-dose, tafamidis,

the acylglucuronide, and a diastereomer of the acylglucuronide were mainly detected, which represented a trace amount to 30%, 33% to 85%, and undetectable to 36% of the total urinary radioactivity, respectively. On the other hand, no radioactive components other than tafamidis were detected in the feces (4.2.2.2.4).

Following a single oral dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 μCi/animal) to bile duct cannulated male and female rats, the cumulative biliary, urinary, and fecal excretion rates of radioactivity up to 72 hours post-dose were 48% to 49%, 19% to 22%, and 21% to 24%, respectively and the total cumulative recovery of radioactivity in the excreta up to 72 hours post-dose (92%-93%) was higher than that in non-cannulated rats (70%-73%). When bile collected up to 24 hours after a single oral dose of 3 mg/kg of ^{14}C-Tafamidis Meglumine (10 μCi/animal) from donor male and female rats was intraduodenally administered to bile duct and duodenum cannulated recipient male and female rats, radioactivity was excreted in the bile and urine by 72 hours post-dose. The above results indicate that tafamidis undergoes enterohepatic recycling (4.2.2.2.4).

Rats during pregnancy and lactation were orally administered 15 mg/kg/day of Tafamidis Meglumine (lactation day 4 and lactation day 11 or 12, ^{14}C-Tafamidis Meglumine, 10 μCi/animal; other days, unlabeled Tafamidis Meglumine) once daily from gestation day 7. Radioactivity was detected in maternal milk at ≥1 hour after administration of ^{14}C-Tafamidis Meglumine and radioactivity levels in the milk and pup plasma and tissue increased up to 24 hours after administration of ^{14}C-Tafamidis Meglumine (4.2.2.3.6).

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Tissue accumulation of tafamidis

PMDA asked the applicant to explain safety in tissues where high levels of tafamidis are distributed.

The applicant explained as follows:

In a distribution study in albino rats (4.2.2.2.4), the organ/plasma ratio of radioactivity was >1 for the liver and harderian glands. Liver findings observed in toxicity studies were single cell necrosis of the liver, increases in ALT, AST, γ-glutamyl transferase (GGT), ALP, and total bilirubin, hepatocellular hypertrophy, increased liver weight, hepatocellular vacuolation, and decreased globulin. These toxicology findings are unlikely to become a major safety problem in humans in light of the following points.

- Since increased liver weight and hepatocellular hypertrophy in rats were reversible and there was a ≥7-fold safety margin relative to the human exposure after repeated administration of 20 mg of Tafamidis Meglumine,[8)] these findings are unlikely to be of clinical relevance.
- Increases in ALT, AST, GGT, ALP and total bilirubin were not associated with histopathological changes and these parameters can be monitored by routine laboratory testing.
- Since hepatocellular vacuolation and decreased globulin were not reproducible at higher doses and longer treatment duration in other studies, these findings are considered of little toxicological significance.
- Since single cell necrosis of the liver occurred in mice and a monoxide metabolite detected was unique to mice, it is inferred that this finding may have been associated with this metabolite.

Adverse events related to hepatic disorders[19] observed in Japanese and foreign clinical studies[20] were as follows: none reported in Study B3461010 (5.3.5.2.3), hepatic enzyme abnormal (1 subject) in the placebo group and hepatomegaly and hepatic enzyme abnormal (1 subject each) in the tafamidis group in Study Fx-005 (5.3.5.1.1), hepatic enzyme abnormal (1 subject) in Study Fx-006 (5.3.5.2.1), and INR increased (1 subject) in Study Fx1A-201 (5.3.5.2.2). There was no trend towards a higher incidence in the tafamidis group than in the placebo group and the reported events were all mild or moderate in severity. Furthermore, according to the foreign post-marketing safety information (November 16, 2011 to November 15, 2012; the estimated total exposure, 165 patient-years), ammonia abnormal (1 subject) was only reported as an adverse event related to hepatic disorders.[19] No clinically relevant events were reported.

A distribution study (4.2.2.2.4) was conducted in albino rats. PMDA asked the applicant to explain the melanin affinity of tafamidis and safety in melanin-containing tissues.

The applicant explained as follows:
An investigation of the melanin affinity of tafamidis has not been performed. In a phototoxicity study in pigmented rats, localized retinopathy and retinal necrosis were observed in all groups including the control group, but there were no treatment-related findings in tissues with high melanin content (4.2.3.7.7.1). Also in dog toxicity studies, there were no treatment-related findings in the skin or eyes (4.2.3.2.5, 4.2.3.2.6). In Japanese and foreign clinical studies,[20] the incidences of skin-related adverse events[21] were 14.3% (1 of 7 subjects) in the placebo group and 45.5% (10 of 22 subjects) in the tafamidis group among non-white races and 14.5% (8 of 55 subjects) in the placebo group and 13.3% (15 of 113 subjects) in the tafamidis group among Caucasians and the incidence tended to be higher in the tafamidis group of non-white races. However, each individual event was reported by 1 or 2 subjects and is not necessarily considered to be specific to non-white races. With respect to eye-related adverse events[22] in Japanese and foreign clinical studies,[20] there was no trend towards differences in incidence between treatment groups or between different races. Based on the above, there should be no major problem with the safety of tafamidis in melanin-containing tissues.

PMDA considers as follows:
Clinical studies and foreign post-marketing safety information indicate no major problems with the safety of tafamidis in the liver that exhibited high levels of radioactivity in a distribution study. However, given that there is no definite evidence that single cell necrosis observed in mice was associated with a metabolite unique to mice (the monoxide) and that there is limited clinical experience with tafamidis, it is necessary to continue to investigate the risk of hepatotoxicity associated with tafamidis via post-marketing surveillance. In addition, regarding the melanin affinity of tafamidis, as there is limited clinical experience with tafamidis in non-white races, it is necessary to continue to collect post-marketing information on the occurrence of skin-related

19) Events in the MedDRA SMQ “drug related hepatic disorders - comprehensive search”
20) Japanese study, 5.3.5.2.3, Study B3461010. Foreign studies, 5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201.
21) Events in the MedDRA SOC “skin and subcutaneous tissue disorders” and HLGT “skin investigations”
22) Events in the MedDRA SOC “eye disorders” and HLT “ophthalmic function diagnostic procedures”

adverse events.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of tafamidis conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (toxicity studies on impurities, a phototoxicity study). As tafamidis is indicated for a serious and ultra-rare disease, the results from a 26-week carcinogenicity study in transgenic mice only were submitted and a 2-year carcinogenicity study in rats is currently ongoing. Given that tafamidis is not considered to have high carcinogenic potential at present, PMDA determined that the carcinogenic potential of tafamidis can be evaluated tentatively, on condition that the results from the rat study are submitted promptly after the completion of the study. Unless otherwise specified, dose levels are expressed as tafamidis (free acid).[1)]

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Acute toxicity assessment in mice (4.2.3.2.1)

Acute toxicity was assessed in mice based on the results from a 28-day oral toxicity study. Mice (CByB6F1, n = 10/sex/group) were orally administered 0 (vehicle control), 10, 30, 45, 60, 120, 240, or 480 mg/kg/day of Tafamidis Meglumine for 28 days (vehicle, 7.5% VE TPGS) and mortality occurred in males at 240 mg/kg/day after Day 3 and at 480 mg/kg/day after Day 2 and in females at 240 mg/kg/day after Day 8 and at 480 mg/kg/day after Day 4. In these treatment groups, as changes in clinical observations, decreased motor activity, impaired gait, seizures, laboured respiration/dyspnea, and hunched appearance etc. were observed. Based on the above results, it was considered that short-term repeated doses of ≥240 mg/kg/day cause mortality in mice.

3.(iii).A.(1).2) Acute toxicity assessment in rats (4.2.3.2.3)

Acute toxicity was assessed in rats based on the results from a 28-day oral toxicity study. Rats (SD, n = 10/sex/group[23)]) were orally administered 0 (vehicle control), 10, 30, 100, or 300 mg/kg/day of Tafamidis Meglumine (vehicle, 0.5% MC) and no acute toxicity-related mortality or changes in clinical observations during early phase of treatment were observed in any of the treatment groups. Based on the above results, the approximate lethal dose in rats was considered to be >300 mg/kg.

3.(iii).A.(1).3) Single-dose toxicity study in dogs (Reference data 4.2.3.1.1)

Dogs (Beagle, 1 male/group, 1 male and 1 female in the 600 mg/kg group only) received a single oral dose of 0 (vehicle control), 30, 100, 300, or 600 mg/kg of tafamidis (vehicle, 0.5% MC). Although loose stool and increased ALP were observed in the male at 600 mg/kg, no mortality occurred and the approximate lethal dose in dogs was considered to be >600 mg/kg.

23) A 14-day recovery period was scheduled for separate recovery animals: n = 5/sex/group for the 0 (vehicle control) and 300 mg/kg/day groups.

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Repeat-dose toxicity studies in rats

3.(iii).A.(2).1).(a) Rat 28-day oral toxicity study with a 14-day recovery period (4.2.3.2.3)

Rats (SD, n = 10/sex/group[23)]) were orally administered 0 (vehicle control), 10, 30, 100, or 300 mg/kg/day of Tafamidis Meglumine for 28 days (vehicle, 0.5% MC). As death occurred frequently at 300 mg/kg/day (7 males and 2 females died or were sacrificed as moribund on Days 8-10), treatment was discontinued on Study Day 8 or 9 and the reversibility of toxicity was evaluated using 5 males and 3 females in the 100 mg/kg/day group. Three females in the 100 mg/kg/day group were sacrificed as moribund on Days 10 to 14 and necropsy revealed marked stomach distension with test article accumulation at ≥100 mg/kg/day. Thus, it was inferred that the inhibition of blood flow associated with this change was related to the deaths. As changes in clinical observations, hunched posture, lethargy, rough hair coat, and urine staining were noted at ≥100 mg/kg/day and scant feces, reddish discharge from nose and eyes, salivation, coldness to touch, and tremors were also observed at 300 mg/kg/day. Body weight gain was reduced at 100 mg/kg/day and body weight was reduced at 300 mg/kg/day and the percent reduction in body weight from baseline to necropsy on Study Day 10 was 9.5% in males and 10.6% in females. Hematological examination revealed decreases in red blood cell parameters (red blood cells, hemoglobin concentration, hematocrit value) and increased reticulocytes in males and decreased reticulocytes and increased monocytes in females at 100 mg/kg/day and in addition to these findings, decreases in white blood cells and lymphocytes and increased neutrophils were noted at 300 mg/kg/day. Clinical chemistry findings included increased creatinine in males at ≥30 mg/kg/day and increases in ALT and total cholesterol in males and increases in creatinine and glucose in females at 100 mg/kg/day. At 300 mg/kg/day, increases in ALT, AST (females only), ALP, urea nitrogen, total cholesterol (males only), GGT (males only), total bilirubin, and triglycerides were observed. As to organ weight measurements, increased liver weights were noted in females at ≥10 mg/kg/day and males at ≥30 mg/kg/day. Histopathological examination revealed lymphoid depletion of the thymus at ≥100 mg/kg/day and lymphoid depletion of the spleen and submandibular lymph nodes at 300 mg/kg/day, and there was an animal with myelosuppression. At 300 mg/kg/day, mucosal necrosis of the glandular stomach and gastrointestinal congestion were also noted and there were animals with findings suggestive of disseminated intravascular coagulation. The applicant determined that the findings observed in this study were all reversible. Based on these results, the applicant determined that the no-observed-adverse-effect level (NOAEL) in this study was 30 mg/kg/day. The C_{max} and AUC at the NOAEL (male/female) were calculated to be 48/52-fold and 37/47-fold the steady state human exposures,[8)] respectively.

3.(iii).A.(2).1).(b) Rat 13-week oral toxicity study with a 4-week recovery period and 26-week oral toxicity study (4.2.3.2.4)

Rats (SD, n = 10/sex/group) were orally administered 0 (vehicle control), 3, 10, or 30 mg/kg/day of Tafamidis Meglumine for 13 or 26 weeks (vehicle, 7.5% VE TPGS) and after 13-week administration, a 4-week recovery period was scheduled for n = 5/sex/group for the control and 30 mg/kg/day groups. There were no toxicity-related deaths. No treatment-related changes in clinical observations or body weight etc. were observed. Clinical chemistry findings at the end of 13-week administration included increased urea nitrogen in males

and increased total bilirubin in females at ≥10 mg/kg/day and increases in ALT and creatinine in males and increases in triglycerides in females at 30 mg/kg/day. At the end of 26-week administration, increased creatinine in females at ≥3 mg/kg/day, increased urea nitrogen in males and increased total bilirubin in females at ≥10 mg/kg/day, and increased creatinine in males at 30 mg/kg/day were observed. As to organ weight measurements, increased liver weights were observed at all dose levels of Tafamidis Meglumine after 13-week administration and at ≥10 mg/kg/day after 26-week administration and decreased kidney weights were also noted in females after 26-week administration. Necropsy and histopathological examination revealed no treatment-related changes. Based on these results, the applicant determined that the NOAEL in this study was 30 mg/kg/day. The C_{max} and AUC at the NOAEL (male/female) were calculated to be 52/69-fold and 42/59-fold the steady state human exposures,[8)] respectively.

3.(iii).A.(2).2) Repeat-dose toxicity studies in dogs

3.(iii).A.(2).2).(a) Dog 28-day oral toxicity study with a 14-day recovery period (4.2.3.2.5)

Dogs (Beagle, n = 3/sex/group) were orally administered 0 (vehicle control), 10, 100, or 300/200 mg/kg/day[24)] of Tafamidis Meglumine for 28 days (vehicle, 0.5% MC) and a 14-day recovery period was scheduled for n = 2/sex/group (only 1 male for the 300/200 mg/kg/day group) for the control and 300/200 mg/kg/day groups. Two males in the 100 mg/kg/day group and 2 males and 1 female in the 300/200 mg/kg/day group died or were sacrificed as moribund. As changes in clinical observations, emesis and abnormal feces were sporadically observed in all groups including the control group and the incidence was higher at ≥100 mg/kg/day. Salivation and lethargy at ≥100 mg/kg/day and thinness, coldness to touch, ataxia, head bobs, and twitching at 300/200 mg/kg/day were observed. Clinical chemistry findings included increases in ALT and ALP in males and decreased calcium in females at ≥100 mg/kg/day and increases in GGT, total bilirubin, and urea nitrogen in males and increased ALP and decreased total cholesterol in females at 300/200 mg/kg/day. As to organ weight measurements, increases in liver and kidney weights and decreased spleen weights in males at 300/200 mg/kg/day were observed. Necropsy of animals that died or were sacrificed as moribund revealed reddish discoloration and thickening in the lungs and the presence of test article in the airway, which were associated with the histopathological findings of diffuse congestion and inflammatory changes with perivascular edema in the lungs. Thus, it seems that these changes were caused by emesis and subsequent aspiration and their relationship to the deaths has been suggested. Based on these results, the applicant determined that the NOAEL in this study was 10 mg/kg/day. The C_{max} and AUC at the NOAEL (male/female) were calculated to be 13/16-fold and 6.1/8.2-fold the steady state human exposures,[8)] respectively.

[24)] As there were animals that were sacrificed as moribund, the high dose was reduced from 300 mg/kg/day to 200 mg/kg/day on Study Day 8 or 9.

3.(iii).A.(2).2).(b) Dog 13-week oral toxicity study with a 4-week recovery period and 39-week oral toxicity study (4.2.3.2.6)

Dogs (Beagle, n = 3/sex/group) were orally administered 0 (vehicle control), 5, 15, or 45 mg/kg/day of Tafamidis Meglumine for 13 weeks or 39 weeks (vehicle; 7.5% VE TPGS was initially used, which was changed to 0.5% MC on Day 48) and after 13-week administration, a 4-week recovery period was scheduled for n = 2/sex/group for the control and 45 mg/kg/day groups. There were no toxicity-related deaths. As changes in clinical observations, mucoid feces, soft feces, emesis, and skin erythema were observed in all groups including the control group and the incidence tended to be higher in the 45 mg/kg/day group. No other treatment-related toxic changes were noted. Based on these results, the applicant determined that the NOAEL in this study was 45 mg/kg/day. The C_{max} and AUC at the NOAEL (male/female) were calculated to be 48/48-fold and 27/34-fold the steady state human exposures[8)], respectively.

3.(iii).A.(3) Genotoxicity

Genotoxicity studies conducted include a bacterial reverse mutation assay (4.2.3.3.1.1), a chromosomal aberration assay with cultured human lymphocytes (4.2.3.3.1.2), and a rat micronucleus assay (4.2.3.3.2.1). In the chromosomal aberration assay with cultured human lymphocytes, there was a trend towards an increased incidence of polyploidy after 4-hour treatment with metabolic activation. However, as structural chromosomal damage was not observed and the micronucleus test was also negative, tafamidis was not considered to have the potential to induce aneuploidy. The applicant concluded that tafamidis is unlikely to have genotoxic potential.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) Tg.rasH2 mouse 26-week oral carcinogenicity study (4.2.3.4.2.1)

Tg.rasH2 mice (n = 25/sex/group) were orally administered 0 (negative control), 0 (vehicle control), 10, 30, or 90 mg/kg/day of Tafamidis Meglumine for 26 weeks (vehicle, 7.5% VE TPGS) or intraperitoneally administered urethane (1000 mg/kg/day) as the positive control on Study Days 1, 3, and 5. There were no increases in treatment-related deaths or treatment-related tumors. The C_{max} and AUC at 90 mg/kg/day (male/female) were calculated to be 39/36-fold and 31/29-fold the steady state human exposures,[8)] respectively.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

3.(iii).A.(5).1).(a) Oral study of fertility and early embryonic development to implantation in rats (4.2.3.5.1.1)

Tafamidis Meglumine was orally administered to rats (SD, n = 25/sex/group) at doses of 0 (vehicle control), 5, 15, or 30 mg/kg/day for 15 days prior to mating, throughout mating, and until gestation day 7 for females and at doses of 0 (vehicle control), 5, 15, or 30 mg/kg/day for 28 days prior to mating, throughout mating, and until the day prior to sacrifice for males (vehicle, 7.5% VE TPGS) and necropsy of females was performed on day 13 of gestation. No toxicity-related deaths occurred. While no treatment-related toxicological findings were observed in males at any dose level, reduced body weight associated with reduced food consumption was

noted during the pre-mating dosing period (Days 1-8) and reduced body weight was sporadically observed also during pregnancy in females in the 30 mg/kg/day group. Based on these results, the applicant determined that the NOAELs were 30 mg/kg/day for male general and reproductive toxicity, 15 mg/kg/day for female general toxicity, 30 mg/kg/day for female reproductive toxicity, and 30 mg/kg/day for early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development studies

3.(iii).A.(5).2).(a) Oral embryo-fetal development study in rats (4.2.3.5.2.2)

Pregnant rats (SD, n = 25/group) were orally administered 0 (vehicle control), 15, 30, or 45 mg/kg/day of Tafamidis Meglumine from gestation day 7 to gestation day 17 (vehicle, 7.5% VE TPGS). Necropsy was performed on day 21 of gestation. Four dams in the 45 mg/kg/day group were sacrificed due to poor general condition on day 13 of gestation. Maternal body weight was transiently decreased at ≥15 mg/kg/day and decreased maternal body weight during early phase of treatment and decreased maternal body weight gain throughout the dosing period at 45 mg/kg/day were observed. In the fetuses, although decreased body weight was noted at ≥30 mg/kg/day, there were no effects on other parameters. Based on these results, the applicant determined that the NOAELs were 30 mg/kg/day for maternal general toxicity, 45 mg/kg/day for maternal reproductive toxicity, and 15 mg/kg/day for embryo-fetal development.

3.(iii).A.(5).2).(b) Oral embryo-fetal development study in rabbits (4.2.3.5.2.4)

Pregnant rabbits (NZW, n = 20/group) were orally administered 0 (vehicle control), 0.5, 2, or 8 mg/kg/day of Tafamidis Meglumine from gestation day 7 to gestation day 19 (vehicle, 7.5% VE TPGS) and necropsied on gestation day 29. Two rabbits in the 8 mg/kg/day group aborted. In the dams, a dose-dependent decrease in body weight at ≥2 mg/kg/day and a transient decrease in body weight and abnormal feces at 8 mg/kg/day were observed. In the fetuses, the number of fetuses with variations or malformations (irregular ossification of the nasal bone or the skull at 0.5 and 2 mg/kg/day, supernumerary ribs at ≥2 mg/kg/day, small eyes and a decreased number of ossified phalanges at 8 mg/kg/day) was increased at ≥2 mg/kg/day and increased resorptions and decreased body weight were also noted at 8 mg/kg/day. Based on these results, the applicant determined that the NOAELs were 0.5 mg/kg/day for maternal general toxicity, 2 mg/kg/day for maternal reproductive toxicity, and <0.5 mg/kg/day for embryo-fetal development. The C_{max} and AUC at 0.5 mg/kg/day were calculated to be 3.1-fold and 2.9-fold the steady state human exposures,[8)] respectively.

3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function

3.(iii).A.(5).3).(a) Oral study for effects on pre- and postnatal development, including maternal function in rats (4.2.3.5.3.1)

Pregnant rats (SD, n = 25/group) were orally administered 0 (vehicle control), 5, 15, or 30 mg/kg/day of Tafamidis Meglumine from gestation day 7 to lactation day 20 (vehicle, 7.5% VE TPGS) and F_0 dams were necropsied on lactation day 21 after natural delivery. In the F_1 generation, after weaning, 25 males and 25 females/group were selected and mated, and then the animals were necropsied after the mating period for males and on gestation day 21 for females. In the F_0 dams, decreased body weight considered associated with

decreased fetal body weight, abandonment of nursing pups, and pup cannibalism at ≥15 mg/kg/day and decreased surviving pups at 30 mg/kg/day were observed. In the F_1 generation, decreased pup body weight and decreased body weight in the post-weaning period as well as poor general condition and decreased pup survival considered associated with abandonment of nursing pups were noted at ≥15 mg/kg/day and all pups died by postnatal day 4 at 30 mg/kg/day. At 15 mg/kg/day, increased incidences of domed head and microphtalmia, poor generation condition such as coarse fur, ataxia, salivation, and coldness to touch, retardation in preputial separation, and impaired water maze learning performance were also observed. In the F_2 generation, female fetal body weight was reduced at 15 mg/kg/day. Based on these results, the applicant determined that the NOAELs were 15 mg/kg/day for maternal general toxicity and 5 mg/kg/day for maternal reproductive toxicity and offspring development.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Toxicity assessment of impurities

Among drug substance impurities, Related Substance A is present in the drug substance at a level greater than the qualification threshold. However, the doses of Related Substance A at the NOAELs in repeat-dose toxicity studies in rats and dogs exceed the estimated maximum human intake level. Thus, the applicant considered that safety qualification for general toxicity can be assured through evaluation of the data from the toxicity studies on Tafamidis Meglumine. As there were no findings suggestive of genotoxic potential at doses greater than the estimated maximum human intake level in a rat micronucleus test and a 26-week carcinogenicity study in Tg.rasH2 mice, the applicant concluded that there is no evidence for the genotoxic potential of impurities.

3.(iii).A.(6).2) Phototoxicity study (4.2.3.7.7.1)

There was no evidence of cutaneous or ocular reactions indicative of phototoxicity in pigmented rats (Long Evans, 5 males/group) treated with a single oral dose of 0 (vehicle control), 10, 30, or 100 mg/kg of Tafamidis Meglumine (vehicle, 7.5% VE TPGS) or 50 mg/kg of 8-methoxypsoralen as a positive control following exposure to simulated sunlight.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Immunotoxicity of tafamidis

With respect to findings such as lymphoid depletion observed in non-clinical studies, a trend towards decreased lymphocytes and an increased risk of infections were observed also in clinical studies of tafamidis. PMDA asked the applicant to explain the immunotoxic potential of tafamidis.

The applicant explained as follows:

Findings such as lymphoid depletion observed in non-clinical studies are thought to be related to stress because (a) the severity of lymphoid depletion was highest in the thymus followed by the spleen and then the lymph nodes, (b) although decreased lymphocytes and increased neutrophils were noted in peripheral blood, neither apparent myelosuppression nor inflammation that would cause increased neutrophils was observed, and (c)

enlarged adrenal gland was observed in some animals. In clinical studies, no major changes in laboratory parameters such as white blood cells and lymphocytes were seen following treatment with tafamidis, while the incidence of infections such as urinary tract infection and vaginal infection tended to be higher with tafamidis. Serious events were also reported [see "4.(iii).B.(3).1) Infections"].

Based on the currently available non-clinical and clinical data, decreases in immune cells such as white blood cells are unlikely to occur in humans, but the immunotoxic potential of tafamidis can not be excluded. On the other hand, since tafamidis may be used also in post-liver transplant patients taking immunosuppressants [see "4.(iii).B.(4).3) Post-liver transplant patients"], the applicant will conduct an immunotoxicity study as soon as possible, and based on the results from this study, will appropriately provide the information on the immunotoxic potential of tafamidis, as needed.

PMDA considers as follows:
Although it is difficult to reach a definitive conclusion on the immunotoxic potential of tafamidis based on the currently presented data, given that the target disease of tafamidis, TTR-FAP, is a progressive, fatal, and rare disease for which the only available treatment alternative is liver transplantation and that the medical need for tafamidis is considered to be high, tafamidis may be approved on condition that an immunotoxicity study is conducted after the market launch, that the information on the study results is provided appropriately, and that the risk of infections associated with tafamidis continues to be investigated via post-marketing surveillance.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

As the evaluation data, the results from foreign food effect studies (5.3.1.2.1, Study Fx-003; 5.3.1.2.2, Study Fx1A-108C) and a foreign bioavailability study (5.3.1.2.3, Study Fx-004) were submitted. Plasma and urine concentrations of tafamidis and metabolites were determined by LC-MS/MS (lower limit of quantification, 2.95-3.00 ng/mL for tafamidis in plasma, 2.95 ng/mL for tafamidis in urine, 50.07 ng/mL for metabolites in urine[25]). In studies with ^{14}C-tafamidis, total radioactivity in plasma, urine, and feces was measured by LSC and tafamidis and metabolite concentrations were determined by radio-HPLC (lower limit of quantification, 3 ng/mL for tafamidis in plasma, 3 ng/mL for tafamidis in urine, 100 ng/g for tafamidis in feces, 50 ng/mL for metabolites in urine[25]). TTR stabilization in plasma was measured by immunoturbidimetry.

In the main clinical studies of tafamidis, the proposed commercial drug product (containing micronized drug substance) and the drug product that has the same formulation as the proposed commercial drug product, but contains non-micronized drug substance (the non-micronized drug product)[26] were used. In some of the foreign clinical studies conducted during the early phase of development, an oral solution formulation, a hard capsule formulation, and a soft capsule formulation containing 10 mg of tafamidis were used.

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[25] As total tafamidis (including metabolites).

[26] No major differences in dissolution profile between the non-micronized drug product and the proposed commercial drug product have been demonstrated.

Dose levels are expressed as the meglumine salt of tafamidis and plasma concentrations are expressed as tafamidis (free acid) and unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Food effects

Following administration of a single oral dose of 20 mg tafamidis solution to foreign healthy male volunteers (19 subjects included in pharmacokinetic assessment) under fasted conditions or after a high-fat meal, the t_{max} of tafamidis occurred 3 hours later and the C_{max} and $AUC_{0\text{-last}}$ were 32.3% and 10.3% lower, respectively, under fed conditions as compared to fasted conditions. The percent stabilization of TTR tetramer[5] under fasted and fed conditions were 50.8% and 30.6%, respectively, at t_{max} and 21.9% and 30.4%, respectively, at 24 hours post-dose (5.3.1.2.1, 5.3.4.1.2).

A single oral dose of 20 mg tafamidis (the proposed commercial drug product) was administered to foreign healthy volunteers (14 subjects included in pharmacokinetic assessment) under fasted conditions or after a high-fat meal and the effects of food on the pharmacokinetics of tafamidis were studied in a crossover design. The plasma tafamidis C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for fed to fasted administration with their 90% confidence intervals were 76.58 [70.49, 83.18] and 92.46 [83.88, 101.93], respectively. The t_{max} of tafamidis was delayed under fed conditions as compared to fasted conditions (1.75 hours under fasted conditions, 4.00 hours under fed conditions). Absorption was delayed and the C_{max} was lowered with a high-fat meal (5.3.1.2.2).

4.(i).A.(2) Bioavailability

Following administration of a single oral dose of the 20, 60, or 120 mg tafamidis hard capsule to foreign healthy male volunteers (12 subjects included in pharmacokinetic assessment) under fasted conditions, the t_{max} of tafamidis in plasma was 6.00 to 7.00 hours and the increases in the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were markedly less than dose-proportional, indicating poor absorption of tafamidis when formulated in a hard capsule. On the other hand, following administration of a single oral dose of 20, 60, or 120 mg tafamidis solution to foreign healthy volunteers[27] (12 subjects included in pharmacokinetic assessment) under fasted conditions, the t_{max} was reduced to 3.00 hours and the C_{max} and $AUC_{0\text{-last}}$ increased 2.67 to 3.27-fold and 1.49 to 2.36-fold, respectively, as compared to administration of the hard capsule. The urinary excretion rate (as total tafamidis) up to 72 hours after the administration of the oral solution was 4.24% to 6.76%, indicating that tafamidis is primarily cleared by biliary excretion. Following administration of the 20, 60, and 120 mg tafamidis hard capsules, the percent stabilization of TTR tetramer[5] was 69%, 144%, and 189%, respectively, at t_{max} and 35%, 73%, and 186%, respectively, at 24 hours post-dose (5.3.3.1.2, 5.3.4.1.1).

Following administration of a single oral dose of 20 mg tafamidis solution, 20 mg tafamidis (the non-micronized drug product) (one 20-mg capsule), or 20 mg tafamidis given as two 10-mg soft capsules to foreign healthy male volunteers (30 subjects included in pharmacokinetic assessment) under fasted conditions, the

[27] 20 mg for female subjects; 60 and 120 mg for male subjects.

plasma tafamidis C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for the non-micronized drug product to the oral solution with their 90% confidence intervals (%) were 92.21 [81.05, 104.91] and 104.94 [83.63, 131.68], respectively, and although the 90% confidence interval for the $AUC_{0\text{-last}}$ did not fall within the range of 0.8 to 1.25, the applicant concluded that there are no clinically significant differences in bioavailability. The plasma tafamidis C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for the 10-mg soft capsule to the oral solution with their 90% confidence intervals (%) were 83.15 [71.18, 97.13] and 89.52 [71.99, 111.33], respectively, and the plasma tafamidis C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for the 10-mg soft capsule to the non-micronized drug product with their 90% confidence intervals (%) were 90.17 [75.69, 107.43] and 85.31 [70.66, 102.99], respectively. Following administration of the oral solution and the non-micronized drug product, the percent stabilization of TTR tetramer[5)] was 77% and 76%, respectively, at t_{max} and 44% and 40%, respectively, at 24 hours post-dose (5.3.1.2.3, 5.3.4.1.3).

4.(i).B Outline of the review by PMDA

In a food effect study with the proposed commercial drug product (5.3.1.2.2), the C_{max} was lowered and the t_{max} was delayed with a high-fat meal. PMDA asked the applicant to explain whether the timing of dosing relative to meals needs to be specified.

The applicant explained as follows:

In this study, although the C_{max} was lowered and the t_{max} was delayed with a high-fat meal, the $AUC_{0\text{-last}}$ was not altered by the presence of food. Based on a population pharmacokinetic (PPK) analysis using pharmacokinetic data from foreign clinical studies (5.3.3.5.2), the steady state C_{max} was 2.59 μg/mL after fasted administration and 2.36 μg/mL after fed administration. Thus, it is unlikely that food significantly affect the efficacy of tafamidis. Based on the above, there is no need to specify the timing of dosing relative to meals in the Dosage and Administration section of the package insert.

PMDA accepted the above explanation.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As the evaluation data, the results from a phase I study in Japanese and foreign healthy volunteers (5.3.3.1.1, Study B3461009), a phase III study in Japanese patients with transthyretin familial amyloid polyneuropathy (TTR-FAP) (5.3.5.2.3, Study B3461010), phase I studies in foreign healthy volunteers (5.3.1.2.3, Study Fx-004; 5.3.3.1.2, Study Fx-002; 5.3.3.1.3, Study Fx1A-107; 5.3.3.4.1, Study Fx1A-109), phase II and phase II/III studies in foreign patients with TTR-FAP (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201), and a study in a special population (5.3.3.3.1, Study Fx1A-105) etc. were submitted. In addition, the results from *in vitro* studies using human biomaterials (Reference data, 4.2.1.2.1, 4.2.2.3.4-4.2.2.4.7, 4.2.2.6.1-4.2.2.6.7) and the results of PPK/pharmacodynamic (PD) analyses of tafamidis in Japanese and foreign subjects (5.3.3.5.1, 5.3.3.5.2) were submitted. Unless otherwise specified, t_{max} is expressed as the median and other pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(ii).A.(1) Studies using human biomaterials

When tafamidis (3-30 μM) was added to Caco-2 cell monolayers derived from a human colorectal carcinoma, the apparent permeability coefficient in the apical to basolateral (A-B) direction was 2.5 to 3.0 × 10^{-5} cm/sec and the apparent permeability coefficient in the basolateral to apical (B-A) direction was 2.6 to 3.0 × 10^{-5} cm/sec and selective inhibitors of P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and organic anion transporting polypeptide (OATP) did not affect the efflux ratio of tafamidis, indicating that these transport systems are not involved in the membrane permeability of tafamidis. On the other hand, the efflux ratios (B-A/A-B) of substrates for P-gp, MRP, OATP, and breast cancer resistance protein (BCRP) were decreased in the presence of 30 μM tafamidis, indicating that tafamidis has an inhibitory effect on the P-gp, MRP, OATP, and/or BCRP transporters (4.2.2.3.1).

When tafamidis (10 μM) was added to human plasma, 600 μM human serum albumin (HSA) solution, and 25 μM human α1-acid glycoprotein (AGP) solution, the percentages of tafamidis bound to human plasma protein, HSA, and AGP were >99.5%, >99.6%, and 12.0%, respectively (4.2.2.3.4).

When tafamidis (0.03-100 μM) was added to 5 μM HSA solution, scatchard plot analysis of tafamidis binding to HSA revealed a dissociation constant (K_D value) of 2.1 μM and a number of binding sites of 2.7 and non-linear regression analysis yielded a K_D value of 2.5 μM (4.2.2.3.5).

When tafamidis (3.6 μg/mL) was added to human plasma in the presence of cyclosporine A (200 ng/mL), tacrolimus (50 ng/mL), prednisone (100 ng/mL), or warfarin (2 μg/mL), the human plasma protein binding of prednisone only was reduced from 78.9% to 68.1% (4.2.2.6.7).

Tafamidis (10 μM) was added to a recombinant human uridine diphosphate-glucuronyltransferase (UGT) (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 2B4, 2B7, 2B15) expression system in the presence of alamethicin and UDPGA to identify UGT isoforms involved in the metabolism of tafamidis, which suggested that the major UGT isoforms responsible for the formation of the acylglucuronide metabolite are UGT1A1, 1A3, and 1A9 (4.2.2.4.11).

Using specific substrates for 6 CYP isoforms (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4/5),[28] CYP inhibition by tafamidis (1-50 μM) in human liver microsomes was evaluated. Although inhibition of CYP2C8 was observed, as the estimated maximum unbound concentration of tafamidis in the liver (0.53 μM) is well below the K_i value, the applicant concluded that clinically significant interactions with drugs that are metabolized by CYP2C8 are unlikely to occur (4.2.2.6.3, 4.2.2.6.4).

Using midazolam, the CYP3A4 induction potential of tafamidis (3.5-70 μM) in cryopreserved human hepatocytes was evaluated. While tafamidis induced CYP3A4 activity (8.61- to 14.26-fold) in hepatocytes

[28] CYP1A2, phenacetin; 2C8, paclitaxel; 2C9, tolbutamide; 2C19, (*S*)-mephenytoin; 2D6, dextromethorphan; 3A4/5, midazolam, testosterone

from 1 of 3 donors, CYP3A4 induction was not observed in hepatocytes from the other 2 donors (4.2.2.6.1).

Using 7-ethoxyresorufin and testosterone, the CYP1A2 and 3A4 induction potential of tafamidis (0.05-50 μM[29]) in primary human hepatocytes was evaluated. Tafamidis did not induce CYP1A2 activity, but induced CYP3A4 activity (1.7- to 7.3-fold) in hepatocytes from 2 of 3 donors (4.2.2.6.5).

Using testosterone, the CYP3A4 induction potential of tafamidis (0.5-50 μM) in primary human hepatocytes in the presence of HSA (40 mg/mL) was evaluated. Minimal induction of CYP3A4 (1.1- to 1.2-fold) was observed in hepatocytes from 1 of 3 donors[30] (4.2.2.6.6).

4.(ii).A.(2) Healthy volunteer studies

Japanese and foreign data

Following administration of a single oral dose of 20 or 40 mg tafamidis (the proposed commercial drug product) to Japanese and foreign healthy male volunteers (12 Japanese subjects and 6 foreign subjects included in pharmacokinetic assessment) under fasted conditions, the pharmacokinetic parameters of tafamidis in plasma were as shown in Table 12. Plasma tafamidis and TTR concentrations and the percent stabilization of TTR tetramer[5] at t_{max} and 24 hours post-dose were as shown in Table 13 and the pharmacokinetics of tafamidis, TTR concentrations, and the percent stabilization of TTR tetramer[5] were similar between Japanese and foreign subjects (5.3.3.1.1).

Table 12. Pharmacokinetic parameters of tafamidis in plasma following administration of a single oral dose of 20 or 40 mg tafamidis to Japanese and foreign healthy male volunteers

Dose	C_{max} (μg/mL)		t_{max} (h)[a]		$t_{1/2}$ (h)		$AUC_{0-\infty}$ (μg·h/mL)	
	Japanese subjects	Foreign subjects	Japanese subjects	Foreign subjects	Japanese subjects	Foreign subjects	Japanese subjects	Foreign subjects
20 mg	1.23 ± 0.19	1.06 ± 0.08	2.5 (2, 4)	3.0 (0.5, 4)	40.7 ± 8.7	40.6 ± 12.0	60.5 ± 9.8	53.7 ± 7.4
40 mg	2.59 ± 0.61	2.19 ± 0.39	3.0 (0.5, 4)	3.0 (1, 4)	40.0 ± 10.2	51.0 ± 13.8	115.3 ± 30.7	95.2 ± 18.5

Mean ± SD
a) Median (Min, Max)

Table 13. Plasma tafamidis and TTR concentrations and percent stabilization of TTR tetramer at t_{max} and 24 hours post-dose

Dose	Timepoint	Tafamidis concentration (μM)		TTR concentration (μM)		Percent stabilization of TTR tetramer (%)	
		Japanese subjects	Foreign subjects	Japanese subjects	Foreign subjects	Japanese subjects	Foreign subjects
20 mg	t_{max}	4.0 ± 0.6	3.4 ± 0.3	4.6 ± 0.6	5.1 ± 0.7	81.1 ± 27.0	73.8 ± 37.7
	24 h	2.4 ± 0.3	2.2 ± 0.1	5.0 ± 0.6	5.4 ± 1.0	50.1 ± 13.1	62.2 ± 5.9
40 mg	t_{max}	8.4 ± 2.0	7.1 ± 1.3	5.1 ± 0.7	4.2 ± 0.2	154.6 ± 37.4	124.7 ± 23.9
	24 h	4.3 ± 0.8	3.4 ± 0.4	5.6 ± 0.9	4.0 ± 0.6	101.2 ± 29.5	99.4 ± 43.7

Mean ± SD

Foreign data

Foreign healthy male volunteers (18 subjects included in pharmacokinetic assessment) were orally administered 15, 30, or 60 mg tafamidis solution once daily for 14 days. The C_{max} (1.75 ± 0.21, 3.32 ± 0.96, and 4.40 ± 1.16 μg/mL, respectively) and $AUC_{0-\tau}$ (30.13 ± 2.76, 66.70 ± 25.46, and 84.33 ± 25.46 μg·h/mL, respectively) of tafamidis in plasma on Day 14 were 1.7- to 2.5-fold and 2.1- to 2.8-fold higher than those on

29) Donor 1, 0.05 to 5.0 μM; Donors 2 and 3, 0.5 to 50 μM.

30) Since adequate induction of CYP3A4 activity by a positive control (rifampicin) was not observed in hepatocytes from the other 2 donors, their data were excluded from evaluation.

Day 1, respectively (the C_{max} on Day 1 was 0.71 ± 0.11, 1.41 ± 0.10, and 2.55 ± 0.54 μg/mL, respectively, and the $AUC_{0-\tau}$ on Day 1 was 11.39 ± 1.18, 24.06 ± 3.87, and 39.78 ± 9.16 μg·h/mL, respectively). On Day 14, the increases in the C_{max} and $AUC_{0-\tau}$ were less than dose-proportional. The percent stabilization of TTR tetramer[5)] at 24 hours post-dose on Day 14 was 57%, 100%, and 132%, respectively. The main component in plasma was tafamidis and an acylglucuronide metabolite was detected (5.3.3.1.2, 5.3.4.1.1, 4.2.2.4.5, 4.2.2.4.6, 4.2.2.4.7).

Following administration of a single oral dose of 20 mg tafamidis solution (containing 50 μCi ^{14}C-tafamidis) to foreign healthy male volunteers (6 subjects included in pharmacokinetic assessment) under fasted conditions, the C_{max} values of tafamidis and total radioactivity in plasma were 1.43 ± 0.09 μg/mL and 1.57 ± 0.11 μg eq./mL, respectively, and the AUC_{0-last} values were 47.52 ± 11.30 μg·h/mL and 65.58 ± 14.91 μg eq.·h/mL, respectively, showing that the main radioactive component in plasma was tafamidis. The urinary, and fecal recoveries of the administered radioactivity up to the last sampling timepoint (360 or 528 hours post-dose) were 22.35 ± 6.94% and 58.50 ± 6.08%, respectively. Two radiolabeled compounds (tafamidis and its glucuronide[31)]) were mainly detected in plasma, urine, and feces and tafamidis represented the major radiolabeled compound in plasma and feces and the major radiolabeled compound in urine was the glucuronide (5.3.3.1.3).

4.(ii).A.(3) Patient studies

Japanese data

Japanese patients with TTR-FAP (10 subjects included in pharmacokinetic assessment: nine V30M patients and one S77Y patient) were orally administered 20 mg tafamidis (the proposed commercial drug product) once daily. The plasma tafamidis concentrations at Weeks 2, 8, and 26 were 2.17 ± 1.62, 2.14 ± 1.36, and 2.22 ± 1.49 μg/mL, respectively, immediately before administration and 2.38 ± 1.90, 2.77 ± 1.78, and 2.74 ± 1.89 μg/mL, respectively, at 3 hours post-dose, showing that plasma tafamidis concentrations were almost constant after Week 2. The plasma tafamidis and TTR concentrations and the percent stabilization of TTR tetramer[5)] at 3 hours post-dose at Weeks 8, 26, and 52 were as shown in Table 14 (5.3.5.2.3).

Table 14. Plasma tafamidis and TTR concentrations and percent stabilization of TTR tetramer in Japanese patients with TTR-FAP

	Tafamidis concentration (μM)		TTR concentration (μM)		Percent stabilization of TTR tetramer (%)	
	V30M	S77Y	V30M	S77Y	V30M	S77Y
N	9	1	9	1	9	1
Week 8	9.4 ± 6.0	5.8	4.5 ± 1.0	3.1	147.3 ± 49.3	352.5
Week 26	9.1 ± 6.5	6.6	4.7 ± 1.3	3.5	173.3 ± 73.0	401.1
Week 52	9.6 ± 7.9	5.5	4.7 ± 1.1	3.3	123.8 ± 62.7	328.4

Mean ± SD

Foreign data

Foreign patients with TTR-FAP (6 subjects included in pharmacokinetic assessment, all V30M patients) were orally administered 20 mg tafamidis (the non-micronized drug product) once daily. The plasma tafamidis concentration at Week 8 was 1.98 ± 0.92 μg/mL. Plasma tafamidis and TTR concentrations and the percent stabilization of TTR tetramer[5)] over time were as shown in Table 15 (5.3.5.1.1).

[31)] The compound was inferred as being a glucuronide of tafamidis by a study using glucuronidase, but could not be identified.

Table 15. Plasma tafamidis and TTR concentrations and percent stabilization of TTR tetramer in foreign patients with TTR-FAP (V30M patients)

	N	Tafamidis concentration (μM)	TTR concentration (μM)	Percent stabilization of TTR tetramer (%)
Week 8	61	7.1 ± 3.2	5.1 ± 0.7	179.9 ± 65.4
Month 6	58	7.0 ± 3.3	5.1 ± 0.8	170.5 ± 69.6
Month 12	45	7.3 ± 3.5	5.0 ± 0.7	157.0 ± 69.6
Month 18	48	7.3 ± 4.1	5.0 ± 0.9	149.7 ± 84.5

Mean ± SD

Foreign patients with TTR-FAP (21 subjects assessed: L58H [4 subjects], F64L [4 subjects], T60A [4 subjects], G47A [3 subjects], I107V [2 subjects], S77Y [2 subjects], D38A [1 subject], S77F [1 subject]) were orally administered 20 mg tafamidis (the non-micronized drug product) once daily. The plasma tafamidis and TTR concentrations and the percent stabilization of TTR tetramer[5)] at Week 6 and Month 12 were as shown in Table 16 (5.3.5.2.2).

Table 16. Plasma tafamidis and TTR concentrations and percent stabilization of TTR tetramer in foreign patients with TTR-FAP (non-V30M patients)

		N	Tafamidis concentration (μM)	TTR concentration (μM)	Percent stabilization of TTR tetramer (%)
Overall population	Week 6	19	8.8 ± 4.9	4.8 ± 1.2	266.2 ± 110.5
	Month 12	15	7.4 ± 2.7	4.5 ± 1.0	242.4 ± 134.4
L58H	Week 6	3	9.1 ± 3.1	5.5 ± 1.1	353.1 ± 59.7
	Month 12	2	9.4, 8.3	6.1, 5.7	393.6, 517.2
F64L	Week 6	4	9.5 ± 6.7	5.1 ± 0.8	290.1 ± 69.5
	Month 12	4	6.2 ± 2.0	4.5 ± 0.5	214.2 ± 90.7
T60A	Week 6	3	7.9 ± 1.6	4.7 ± 0.7	266.0 ± 16.6
	Month 12	3	7.9 ± 1.1	4.6 ± 0.9	225.8 ± 50.9
G47A	Week 6	3	6.5 ± 1.8	4.2 ± 0.9	236.1 ± 192.8
	Month 12	1	4.8	4.6	114.5
I107V	Week 6	2	7.4, 3.4	7.5, 3.3	281.4, 88.6
	Month 12	2	5.7, 3.1	6.0, 3.4	380.1, 49.7
S77Y	Week 6	2	23.6, 8.5	5.5, 3.3	347.9, 56.1
	Month 12	2	13.6, 8.1	4.3, 3.6	289.3, 41.1
S77F	Week 6	1	8.0	2.9	358.7
	Month 12	1	10.0	2.9	316.5
D38A	Week 6	1	8.4	5.1	198.7

Mean ± SD, Individual measurements are listed for the timepoints at which data from ≤2 subjects are available.

4.(ii).A.(4) Intrinsic factor pharmacokinetic studies

4.(ii).A.(4).1) Effect of hepatic function (5.3.3.3.1)

Following administration of a single oral dose of 20 mg tafamidis (the non-micronized drug product) to foreign healthy adult subjects (16 subjects) and subjects with hepatic impairment (mild [Child-Pugh Score of 5-6] and moderate [Child-Pugh Score of 7-9], 9 subjects each) under fasted conditions, the pharmacokinetic parameters of tafamidis in plasma were as shown in Table 17. While no major differences were observed for the C_{max}, the $AUC_{0\text{-last}}$ was 17% and 35% lower in subjects with mild hepatic impairment and subjects with moderate hepatic impairment compared to healthy adult subjects, respectively. The $t_{1/2}$ was reduced in subjects with moderate hepatic impairment.

Table 17. Pharmacokinetic parameters of tafamidis in plasma following administration of a single oral dose of tafamidis to foreign healthy adult subjects and subjects with hepatic impairment

	N	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (μg·h/mL)	CL/F (L/h)
Healthy adult subjects	16	1.28 ± 0.30	2.00	52.43 ± 16.10	66.02 ± 17.55	0.32 ± 0.10
Subjects with mild hepatic impairment	9	1.11 ± 0.20	3.00	56.35 ± 17.99[a)]	54.53 ± 12.68	0.38 ± 0.10[a)]
Subjects with moderate hepatic impairment	9	1.38 ± 0.56	1.00	45.10 ± 11.85[b)]	42.84 ± 12.92	0.52 ± 0.11[b)]

Mean ± SD
a) N = 8 b) N = 5

4.(ii).A.(5) PPK and population pharmacokinetic/pharmacodynamic (PPK/PD) analyses

Using the plasma tafamidis concentration data obtained from phase I and phase III studies in Japanese and foreign subjects (5.3.3.1.1, Study B3461009; 5.3.5.2.3, Study B3461010) (28 subjects [12 Japanese healthy volunteers, 6 foreign healthy volunteers, 10 Japanese patients with TTR-FAP], 378 sampling points), PPK analysis[32)] was performed. The pharmacokinetics of tafamidis in plasma were described by a 2-compartment model and the effect of food on absorption rate constant (k_a) and the effect of body weight on oral clearance (CL/F) were identified as significant factors influencing the pharmacokinetics of tafamidis. In addition, using the plasma tafamidis concentration and TTR percent stabilization[5)] data obtained from these clinical studies (28 subjects, 56 sampling points), PPK/PD analysis[32)] was performed. As a result, the relationship between plasma tafamidis:TTR molar ratio and the percent stabilization of TTR tetramer[5)] was described by an E_{max} model and the model parameters were estimated as follows: $E_{max} = 202 \times \theta$ (healthy volunteers, 1; TTR-FAP patients, 1.23), $EC_{50} = 0.959$, and $\gamma = 1.46$ (5.3.3.5.1).

Using the plasma tafamidis concentration data (268 subjects [109 healthy volunteers, 124 patients with TTR-FAP, 35 patients with TTR-CM], 3394 sampling points) obtained from 11 foreign clinical studies in healthy volunteers, patients with TTR-FAP, and patients with transthyretin amyloid cardiomyopathy (TTR-CM) (5.3.1.2.1, Study Fx-003; 5.3.1.2.2, Study Fx1A-108C; 5.3.1.2.3, Study Fx-004; 5.3.3.1.2, Study Fx-002[33)]; 5.3.3.1.3, Study Fx1A-107; 5.3.3.3.1, Study Fx1A-105; 5.3.3.4.1, Study Fx1A-109; 5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201, Study Fx1B-201[34)]), PPK analysis[35)] was performed. The pharmacokinetics of tafamidis in plasma were described by a 2-compartment model, and the effects of food and formulation on k_a and the effects of body weight and age on CL/F were identified as significant factors influencing the pharmacokinetics of tafamidis. In addition, the plasma tafamidis concentration and TTR percent stabilization data from 247 subjects (69 healthy volunteers, 143 patients with TTR-FAP, 35 patients with TTR-CM) (970 sampling points) in 7 studies that evaluated TTR stabilization (5.3.1.2.1, Study Fx-003; 5.3.1.2.3, Study Fx-004; 5.3.3.1.2. Study Fx-002[33)]; 5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201, Study Fx1B-201[34)]), were used to perform PPK/PD analysis.[35)] As a result, the relationship between plasma tafamidis:TTR molar ratio and the percent stabilization of TTR tetramer was described by an E_{max} model and the model parameters were estimated as follows: $E_{max} = \theta$ (healthy volunteers, 137; patients with wild-type TTR,[34)] 168; patients with variant TTR, 242), $EC_{50} = 0.831$, and $\gamma = 1.36$ (5.3.3.5.2).

32) NONMEM version 6 level 2.0 was used.

33) Only data for 15, 20, or 30 mg/day tafamidis solution were included in analysis.

34) A clinical study in foreign patients with TTR-CM.

35) NONMEM version 7 level 1.0 was used.

4.(ii).A.(6) Drug-drug interaction study

Foreign healthy volunteers (16 subjects included in pharmacokinetic assessment) were orally administered a single dose of 7.5 mg midazolam on Day 1, 20 mg tafamidis (the proposed commercial drug product) once daily from Day 2 to Day 14, and 7.5 mg midazolam and 20 mg tafamidis on Day 15 (both under fasted conditions). The midazolam C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for Day 1 to Day 15 with their 90% confidence intervals were 110.8 [98.7, 124.4] and 108.4 [101.1, 116.2], respectively, and coadministration with tafamidis had no effects on plasma midazolam concentrations (5.3.3.4.1).

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetics and TTR stabilization in patients with hepatic impairment

Since the primary clearance mechanism for tafamidis is glucuronidation in the liver and tafamidis is expected to be used in patients with hepatic impairment including post-liver transplant patients, PMDA asked the applicant to explain the pharmacokinetics of tafamidis and the percent stabilization of TTR tetramer in patients with hepatic impairment.

The applicant explained as follows:

A clinical pharmacology study in foreign subjects with mild or moderate hepatic impairment (Study Fx1A-105, 5.3.3.3.1) showed that the CL/F of tafamidis in plasma increased (mild impairment, 19% increase; moderate impairment, 68% increase) and the $AUC_{0\text{-last}}$ decreased (mild impairment, 16% decrease; moderate impairment, 36% decrease) with increasing severity of hepatic impairment (Table 17): The concentrations of plasma proteins, such as TTR and albumin, were decreased in subjects with hepatic impairment (Table 18) and a lower fraction of plasma protein-bound tafamidis resulted in a higher apparent clearance. Thus, a safety problem due to increases in the plasma tafamidis concentration is unlikely to occur in patients with mild or moderate hepatic impairment. Taking into account the mechanism of action of tafamidis, the efficacy of tafamidis should depend on not only plasma tafamidis concentrations, but also plasma TTR concentrations. For the efficacy of tafamidis in patients with mild or moderate hepatic impairment, the plasma tafamidis and TTR concentrations at 24 hours after administration of tafamidis in Study Fx1A-105 (5.3.3.3.1) were as shown in Table 18, demonstrating that the plasma tafamidis:TTR concentration ratio in subjects with mild or moderate hepatic impairment was equal to or greater than that in healthy adult subjects. Therefore, the efficacy of tafamidis 20 mg/day once daily can be expected also in these patients.

Table 18. Plasma tafamidis and TTR concentrations at 24 hours after administration of a single oral dose of tafamidis to foreign healthy adult subjects and subjects with hepatic impairment

	N	Plasma tafamidis concentration (μM)	Plasma TTR concentration (μM)	Tafamidis:TTR molar ratio	Plasma albumin concentration (mg/dL)
Healthy adult subjects	16	2.09 ± 0.40	4.97 ± 0.91	0.43 ± 0.08	36.5 ± 1.88[a)]
Subjects with mild hepatic impairment	9	1.85 ± 0.31	4.60 ± 0.63[b)]	0.41 ± 0.06[b)]	36.1 ± 3.44[b)]
Subjects with moderate hepatic impairment	9	1.74 ± 0.48	2.01 ± 1.02	1.10 ± 0.80	21.9 ± 9.39

Mean ± SD
a) N = 15, b) N = 8

In patients with severe hepatic impairment, tafamidis exposure is unlikely to be increased, based on the results from Study Fx1A-105 (5.3.3.3.1). However, as the information on the pharmacokinetics of tafamidis in this patient population is not available at present, after a system to allow measurement of plasma tafamidis concentrations in response to the physician's request will be in place, data will be collected via post-marketing surveillance. In addition, the package insert will advise that tafamidis should be administered with care in patients with severe hepatic impairment, taking into consideration that there is no clinical experience with tafamidis in clinical studies.

PMDA considers as follows:
Based on the submitted study data, if tafamidis is administered to patients with mild or moderate hepatic impairment without dosage adjustment, a clinically significant problem is unlikely to occur. On the other hand, in patients with severe hepatic impairment, the effect of further deterioration of hepatic function on the concentrations of plasma proteins such as TTR and albumin is unknown, and whether the apparent clearance of tafamidis increases as in patients with mild or moderate hepatic impairment is also unknown. However, given that the target disease of tafamidis, TTR-FAP, is a progressive, fatal, and rare disease for which the only available treatment alternative is liver transplantation; that the medical need for tafamidis is high; and that plasma tafamidis concentrations in patients with severe hepatic impairment can be measured as needed, tafamidis may be used with care in patients with severe hepatic impairment, instead of limiting the use of tafamidis. It is necessary to continue to investigate the efficacy, safety, and pharmacokinetics of tafamidis in patients with severe hepatic impairment via post-marketing surveillance and assess the effect of hepatic impairment (including mild and moderate hepatic impairment) on the efficacy and safety of tafamidis.

4.(ii).B.(2) Risk of QT/QTc interval prolongation and proarrhythmia
Based on the ICH E14 guideline "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (PFSB/ELD Notification No.1023-1 dated October 23, 2009), PMDA asked the applicant to explain the risk of QT/QTc interval prolongation and proarrhythmia associated with tafamidis.

The applicant explained as follows:
A thorough QT/QTc study in accordance with this guideline (Study B3461031) is currently ongoing and the study results will become available in September 2013. The findings described below indicate that the risk of QT/QTc interval prolongation and proarrhythmia associated with tafamidis is not high. Also, since the target disease is a progressive, fatal, and rare disease, it should be appropriate to provide tafamidis to clinical practice even before the results from a thorough QT/QTc study become available.

- Tafamidis did not inhibit hERG current in a non-clinical study (4.2.1.3.2) and abnormal ECG or QT/QTc prolongation was not observed in dogs following a single oral dose of 300 mg/kg of tafamidis (4.2.1.3.3).
- Plasma tafamidis concentrations were not correlated with change from baseline in QTcF interval in Japanese and foreign clinical studies (5.3.5.2.3, Study B3461010; 5.3.3.3.1, Study Fx1A-105; 5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201).

- Based on the incidence of new abnormal ECGs detected after the start of treatment with tafamidis in a Japanese phase III study (5.3.5.2.3, Study B3461010) and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201) (Table 19), Study Fx-005 showed no greater risk of many events in the tafamidis group than in the placebo group and a trend towards a higher incidence of rhythm disturbance in the tafamidis group, which is inferred to be attributable to pacemaker insertion for liver transplantation (5 of 8 subjects with the event). The incidences of arrhythmia and QTcB >500 msec tended to be higher in Study Fx1A-201 in patients with non-V30M mutations (non-V30M patients) compared to clinical studies in patients with the V30M mutation (V30M patients), which is inferred to be attributable to the progression of amyloid cardiomyopathy because amyloid cardiomyopathy is prominent in non-V30M patients compared to V30M patients.

Table 19. Incidence of new abnormal ECGs detected after the start of treatment with tafamidis

	Study B3461010	Study Fx-005		Study Fx-006	Study Fx1A-201
		Placebo	Tafamidis		
Electrocardiogram abnormal	100.0 (1/1)	13.2 (5/38)	5.1 (2/39)	23.1 (12/52)	66.7 (4/6)
Arrhythmia	0	9.8 (6/61)	9.5 (6/63)	0	50.0 (9/18)
Rhythm disturbance	0	7.8 (4/51)	13.8 (8/58)	12.2 (9/74)	11.1 (2/18)
Conductance abnormality	0	15.9 (7/44)	4.5 (2/44)	11.7 (7/60)	25.0 (2/8)
Morphology abnormality	0	1.6 (1/62)	1.5 (1/65)	2.4 (2/85)	0
ST segment abnormality	0	1.6 (1/62)	0	1.2 (1/84)	5.0 (1/20)
T wave abnormality	0	5.0 (3/60)	0	14.5 (12/83)	11.1 (2/18)
ΔQTcB ≥60 msec	0	3.2 (2/63)	1.6 (1/64)	1.2 (1/85)	0
ΔQTcF ≥60 msec	0	1.6 (1/63)	0	1.2 (1/85)	0
QTcB >500 msec	10.0 (1/10)	1.6 (1/62)	4.8 (3/62)	2.5 (2/81)	10.5 (2/19)
QTcF >500 msec	10.0 (1/10)	1.6 (1/62)	4.7 (3/64)	0	5.0 (1/20)

Incidence (No. of subjects with event/No. of subjects assessed)
Analysis population: subjects with no abnormalities at baseline in each category

- With respect to the occurrence of adverse events related to QT/QTc interval prolongation and proarrhythmia[36] in a Japanese phase III study (5.3.5.2.3, Study B3461010) and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.1, Study Fx-006; 5.3.5.2.2, Study Fx1A-201), the incidence was only 10.0% (loss of consciousness [1 subject]) in Study B3461010 (5.3.5.2.3), 4.8% (syncope [3 subjects]) in the placebo group and 1.5% (syncope [1 subject]) in the tafamidis group in Study Fx-005 (5.3.5.1.1), 2.4% (ventricular tachycardia and syncope, 1 subject each) in Study Fx-006 (5.3.5.2.1), and 9.5% (ventricular tachycardia and syncope, 1 subject each) in Study Fx1A-201 (5.3.5.2.2), showing that there was no trend towards a higher incidence in the tafamidis group compared to the placebo group.
- A certain number of TTR-FAP patients have cardiac impairment due to cardiomyopathy secondary to TTR-derived amyloid deposition in the myocardium (Ando Y, et al. *Rare/Intractable Disease Project supported by the Health and Labour Sciences Research Grant: Amyloidosis Research Committee, 2010 Clinical Practice Guideline for Amyloidosis*, 2010;20-26), but there were no major differences in the

[36] Events in the MedDRA SMQ "Torsade de pointes/QT prolongation" and PTs: epilepsy; temporal lobe epilepsy; status epilepticus; petit mal epilepsy; frontal lobe epilepsy; myoclonic epilepsy; epileptic psychosis; generalised non-convulsive epilepsy; partial seizures; infantile spasms; simple partial seizures; complex partial seizures; epileptic aura; clonic convulsion; tonic convulsion; convulsions local; acquired epileptic aphasia; grand mal convulsion; atonic seizures; drop attacks; postictal state; atypical benign partial epilepsy; convulsion; and sudden unexplained death in epilepsy.

incidences of the above-mentioned abnormal ECG and adverse events related to QT/QTc interval prolongation and proarrhythmia[36] according to the presence or absence of cardiovascular complications.

PMDA considers as follows:

Since a certain number of TTR-FAP patients (the intended population for tafamidis) have cardiac impairment due to cardiomyopathy secondary to amyloid deposition in the myocardium, a thorough QT/QTc study should have been completed before regulatory submission and the risk of QT/QTc interval prolongation and proarrhythmia associated with tafamidis should have fully been assessed. However, while there is limited clinical experience with tafamidis in Japanese and foreign clinical studies, the currently available non-clinical and clinical study data have not suggested a risk of QT/QTc interval prolongation and proarrhythmia associated with tafamidis. In addition, the target disease of tafamidis, TTR-FAP, is a progressive, fatal, and rare disease for which the only available treatment alternative is liver transplantation, and therefore the medical need for tafamidis is high. Taking account of these points, tafamidis can be provided to medical practice at present, on condition that necessary safety measures are taken as soon as the results from the currently ongoing thorough QT/QTc study (Study B3461031) become available.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the efficacy and safety evaluation data, the results from a Japanese phase III study in Japanese patients with TTR-FAP (V30M patients and non-V30M patients) (5.3.5.2.3, Study B3461010), a foreign phase II study in foreign patients with TTR-FAP (non-V30M patients) (5.3.5.2.2, Study Fx1A-201), and a foreign phase II/III study in foreign patients with TTR-FAP (V30M patients) (5.3.5.1.1, Study Fx-005) and its foreign long-term extension study (5.3.5.2.1, Study Fx-006) were submitted. As the safety evaluation data, the results from a phase I study in Japanese and non-Japanese healthy male volunteers living in the US (5.3.3.1.1, Study B3461009) and phase I studies in foreign healthy volunteers (5.3.1.2.1, Study Fx-003; 5.3.1.2.2, Study Fx1A-108C; 5.3.1.2.3, Study Fx-004; 5.3.3.1.2, Study Fx-002; 5.3.3.1.3, Study Fx1A-107; 5.3.3.4.1, Study Fx1A-109) etc. were submitted. As the reference data, the results from a long-term extension study in foreign patients with TTR-FAP (V30M patients and non-V30M patients) (Reference data 5.3.5.2.4, Fx1A-303) were submitted. As the pivotal studies, Study B3461009 (5.3.3.1.1), Study Fx1A-201 (5.3.5.2.2), Study Fx-005 (5.3.5.1.1), and Study B3461010 (5.3.5.2.3) are summarized below.

4.(iii).A.(1) Phase I study

4.(iii).A.(1).1) Phase I single-dose study (5.3.3.1.1, Study B3461009 [July 2011 to August 2011])

A randomized, double-blind, placebo-controlled study was conducted in Japanese and non-Japanese healthy male volunteers living in the US (Target sample size of 21; 14 Japanese subjects and 7 non-Japanese subjects) to evaluate the safety, pharmacokinetics, and percent stabilization of TTR tetramer[5] following a single oral dose of tafamidis [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics and the percent stabilization of TTR tetramer[5]].

A single oral dose of placebo or 20 or 40 mg of tafamidis was to be administered under fasted conditions.

All of 21 treated subjects (14 Japanese subjects [2 subjects in the placebo group, 6 subjects each in the 20 and 40 mg groups], 7 non-Japanese subjects [1 subject in the placebo group, 3 subjects each in the 20 and 40 mg groups]) were included in the safety population.

Adverse events (including laboratory abnormalities) occurred in 2 subjects in the 20 mg group (headache [2 non-Japanese subjects]) and a causal relationship to study drug could not be denied for both cases. No deaths or other serious adverse events were reported.

As to vital signs (blood pressure and pulse rate), blood pressure diastolic increased (1 Japanese subject in the 20 mg group), blood pressure diastolic decreased (3 Japanese subjects in the 40 mg group), and blood pressure systolic decreased (1 Japanese subject in the 40 mg group) were observed. No clinically significant changes in ECG were reported.

Based on the above, the applicant explained that there should be no major problem with the safety of a single oral dose of 20 or 40 mg of tafamidis in Japanese and non-Japanese healthy male volunteers living in the US.

4.(iii).A.(2) Exploratory study

4.(iii).A.(2).1) Foreign phase II study (5.3.5.2.2, Study Fx1A-201 [June 2008 to January 2010])

An open-label, uncontrolled study was conducted in foreign TTR-FAP patients with non-V30M mutations (Target sample size of 24) to determine the percent stabilization of TTR tetramer[5)] and evaluate the efficacy, safety, and pharmacokinetics of tafamidis [see "4.(ii) Summary of clinical pharmacology studies" for the percent stabilization of TTR tetramer[5)] and pharmacokinetics].

Tafamidis 20 mg/day was to be orally administered once daily. The duration of treatment was 12 months and subjects with a TTR percent stabilization[5)] of ≤32%[37)] at Week 6 were to be discontinued from the study.

All of 21 treated subjects (L58H [4 subjects], F64L [4 subjects], T60A [4 subjects], G47A [3 subjects], I107V [2 subjects], S77Y [2 subjects], D38A [1 subject], S77F [1 subject]) were included in the safety population and the ITT (Intent-to-Treat) population for efficacy analyses. Of these subjects, 3 subjects discontinued and the reasons for discontinuations were liver transplantation (2 subjects) and an adverse event (1 subject).

The results of the efficacy endpoints were as follows: the Neuropathy Impairment Score-Lower Limb (NIS-LL)[38)] change from baseline to Month 12 was 2.7 ± 6.21 and the change from baseline to Month 12 in the Total

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[37)] Although the applicant explained that this cut-off value was derived from the upper limit of the percent stabilization of TTR tetramer[5)] (32%) in placebo-treated subjects in Study Fx-002 (5.3.3.1.2), since this value could not be reproduced by the applicant (actually 26%) in the course of a regulatory review, it was justified 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 (5.3.5.1.1). It has been confirmed that even when the cut-off value is changed to 26%, the study outcomes are almost unaffected.

[38)] The NIS is a clinical measure that assesses overall neuropathic impairment by scoring for assessments of cranial nerve, muscle weakness, reflexes,

Quality of Life (TQOL) score [39)] as measured by the Norfolk Quality of Life-Diabetic Neuropathy Questionnaire was 0.1 ± 18.01 (mean ± SD). The proportion of subjects with a TTR percent stabilization[5)] of >32%[37)] was 94.7% (18 of 19 subjects[40)]) at Week 6 and 100% (17 of 17 subjects) at Month 12.

The incidence of adverse events (including laboratory abnormalities) was 81.0% (17 of 21 subjects), but no deaths were reported. Other serious adverse events occurred in 8 subjects (ankle fracture and arthritis; malaise, fall, urinary retention, and faecaloma; subileus; carpal tunnel decompression; coronary artery stenosis; transient ischaemic attack; atrioventricular block; and fall and avulsion fracture, 1 subject each) and a causal relationship to study drug could not be denied for ankle fracture (1 subject), malaise and urinary retention (1 subject), and transient ischaemic attack (1 subject).

The incidence of adverse events (including laboratory abnormalities) for which a causal relationship to study drug could not be denied was 38.1% (8 of 21 subjects; diarrhoea, vomiting, neuralgia, and paraesthesia, 2 subjects each, etc.).

There were no clinically significant changes in vital signs (blood pressure, pulse rate, body temperature, respiratory rate). New abnormal ECGs detected after the start of treatment were as shown in Table 19.

Based on the above, the applicant explained that the efficacy of tafamidis 20 mg/day has been suggested and there should be no major safety problem in TTR-FAP patients with non-V30M mutations.

4.(iii).A.(3) Confirmatory study

4.(iii).A.(3).1) Foreign phase II/III study (5.3.5.1.1, Study Fx-005 [January 2007 to May 2009])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in foreign TTR-FAP patients with the V30M mutation (Target sample size of 120; 60 subjects per group) to evaluate the efficacy, safety, and pharmacokinetics of tafamidis and determine the percent stabilization of TTR tetramer[5)] [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics and the percent stabilization of TTR tetramer[5)]].

Placebo or tafamidis 20 mg/day was to be orally administered once daily and the duration of treatment was 18 months.

All of 128 treated subjects (63 subjects in the placebo group, 65 subjects in the tafamidis group) were included

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and sensation (cranial nerve and muscle weakness are scored on a 8-point scale, ranging from 0 to 4; reflexes and sensation are scored on a 3-point scale, ranging from 0 to 2) and the NIS-LL is the lower limb component of the NIS (muscle weakness and reflexes in the lower limbs and sensation of the great toes) (a score ranging from 0 [normal] to 88 [total impairment]).

39) A patient reported outcome assessment to evaluate the patient's perception of neuropathy and its impact on QOL (a score ranging from -2 [best possible QOL] to 138 [worst possible QOL]).

40) TTR stabilization at Week 6 was determined for 19 subjects excluding 1 subject who prematurely discontinued and 1 subject with no FOI at baseline. As a result, one G47A patient had a TTR percent stabilization of <32%. However, when the subject's analysis results at Week 6 became available, the subject had already completed 3-month treatment and the percent stabilization of TTR tetramer was >32% and no adverse events for which a causal relationship to study drug could not be denied were observed. Thus, it was decided to continue treatment of this subject as well.

in the safety population and 125 subjects excluding 3 subjects with no post-baseline efficacy assessment (61 subjects in the placebo group, 64 subjects in the tafamidis group) were included in the ITT population[41] for efficacy analyses. Of the safety population, 37 subjects discontinued (19 subjects in the placebo group, 18 subjects in the tafamidis group) and the main reasons for discontinuations were liver transplantation (13 subjects each in the placebo and tafamidis groups), adverse events (3 subjects in the placebo group, 4 subjects in the tafamidis group), etc.

The co-primary endpoints[42] of the percentage of NIS-LL responders[43] at Month 18 and the change from baseline to Month 18 in the TQOL score in the ITT population were as shown in Table 20 and Table 21, respectively and no statistically significant differences were observed between the placebo and tafamidis groups for both co-primary endpoints, whereas the percentage of NIS-LL responders tended to be higher in the tafamidis group and the change from baseline in the TQOL score tended to be smaller in the tafamidis group.

Table 20. Percentage of NIS-LL responders (ITT, LOCF)

	N	NIS-LL score		% of responders (No. of responders)[b]	Treatment difference [95% CI]	*P*-value[c]
		Baseline	End of study[a]			
Placebo	61	11.4 ± 13.5	17.0 ± 18.9	29.5 (18)	15.8 [-0.92, 32.5]	0.0682
Tafamidis	64	8.36 ± 11.4	9.5 ± 11.9	45.3 (29)		

Mean ± SD
a) Subjects with baseline assessments only (4 subjects each in the placebo and tafamidis groups) were excluded.
b) Dropouts due to death or liver transplantation were categorized as non-responders.
c) Chi-square test

Table 21. TQOL change (ITT, LOCF)

	N	TQOL score		Change[a]	Treatment difference [95% CI][b]	*P*-value[b]
		Baseline	End of study			
Placebo	61	30.8 ± 26.7	37.7 ± 27.9	7.2 ± 2.4	-5.2 [-11.8, 1.3]	0.1157
Tafamidis	64	27.3 ± 24.2	29.7 ± 26.7	2.0 ± 2.3		

Mean ± SD
a) Least-squares mean ± standard error (SE)
b) Analysis of covariance (ANCOVA) with treatment as a factor and baseline score as a covariate

Adverse events occurred in 96.8% of the placebo group (61 of 63 subjects) and 92.3% of the tafamidis group (60 of 65 subjects), but no study-related death was reported.[44] Other serious adverse events occurred in 5 subjects in the placebo group (staphylococcal infection, cellulitis, lymphangitis, and skin ulcer; syncope, anaemia, and oedema peripheral; pneumothorax and cardiac amyloidosis; nausea, vomiting, and catheter site phlebitis; and hypertensive emergency and burns third degree, 1 subject each) and 6 subjects in the tafamidis group (urinary tract infection; urticaria; viral infection; pneumonia and urinary tract infection; localised infection; and conduction disorder, 1 subject each) and a causal relationship to study drug could not be denied for syncope and anaemia (1 subject) and vomiting (1 subject) in the placebo group and urinary tract infection

41) For Study Fx-005, the ITT population was defined as all randomized subjects who received at least one dose of study drug and had at least one post-baseline efficacy assessment for both NIS-LL and Norfolk QOL-DN or discontinued the study due to death or liver transplant.

42) If statistically significant differences were observed between the placebo and tafamidis groups (a two sided significance level of 5%) for both co-primary endpoints (the percentage of NIS-LL responders at Month 18 and the change from baseline to Month 18 in the TQOL score), it could be concluded that the efficacy of tafamidis was confirmed.

43) Subjects with an increase from baseline in NIS-LL of <2 points. Note that subjects who discontinued due to liver transplantation or death were categorized as non-responders.

44) Among patients who underwent liver transplantation after study discontinuation, 3 subjects in the placebo group (post-transplant hepatic failure, post-transplant sepsis, and unknown cause of death, 1 subject each) and 1 subject in the tafamidis group (cardiac tamponade) died, but a causal relationship to study drug was denied for all cases.

(1 subject) and urticaria (1 subject) in the tafamidis group.

Adverse events (including laboratory abnormalities) for which a causal relationship to study drug could not be denied occurred in 68.3% of the placebo group (43 of 63 subjects) and 60.0% of the tafamidis group (39 of 65 subjects) and the main events were urinary tract infection (0 subjects in the placebo group, 7 subjects in the tafamidis group), diarrhoea (7 subjects in the placebo group, 6 subjects in the tafamidis group), headache (10 subjects in the placebo group, 5 subjects in the tafamidis group), pain in extremity (3 subjects in the placebo group, 5 subjects in the tafamidis group), abdominal pain upper (2 subjects in the placebo group, 5 subjects in the tafamidis group), nausea (6 subjects in the placebo group, 4 subjects in the tafamidis group), vomiting (5 subjects in the placebo group, 3 subjects in the tafamidis group), neuralgia (7 subjects in the placebo group, 1 subject in the tafamidis group), oedema peripheral and muscle spasms (5 subjects in the placebo group, 1 subject in the tafamidis group), constipation (4 subjects in the placebo group, 1 subject in the tafamidis group), paraesthesia (6 subjects in the placebo group, 0 subjects in the tafamidis group), and fatigue (5 subjects in the placebo group, 0 subjects in the tafamidis group) etc.

There were no clinically significant changes in vital signs (blood pressure, pulse rate, body temperature, respiratory rate). New abnormal ECGs detected after the start of treatment were as shown in Table 19. New abnormal echocardiograms detected after the start of treatment were as shown in Table 22.

Table 22. New abnormal echocardiograms detected after start of treatment

	Placebo	Tafamidis
Echocardiogram abnormal	84.2 (16/19)	76.0 (19/25)
Left ventricular posterior wall thickness ≥13 mm	4.0 (2/50)	1.7 (1/58)
Left ventricular septal thickness ≥13 mm	4.2 (2/48)	3.5 (2/57)
Right ventricular thickness ≥7 mm	5.7 (3/53)	5.7 (3/53)
E/A ratio ≥2	11.8 (6/51)	8.5 (5/59)
E/E prime (lateral wall) >15	3.8 (2/52)	1.8 (1/57)
E/E prime (septal wall) >15	4.2 (2/48)	3.8 (2/52)
Deceleration time of the E wave ≤150 msec	10.9 (5/46)	6.1 (3/49)
Isovolumic relaxation time ≤70 msec	41.2 (7/17)	52.9 (9/17)
Valvular thickness	31.1 (14/45)	22.4 (11/49)
Abnormal respiratory variation of inferior vena cava	6.7 (4/60)	0 (0/63)
Pericardial effusion	11.9 (7/59)	4.9 (3/61)

Incidence (No. of subjects with abnormality/No. of subjects assessed)
Analysis population: subjects with no abnormalities at baseline in each category

Based on the above, the applicant explained that the efficacy of tafamidis 20 mg/day has been suggested and there should be no major safety problem in TTR-FAP patients with the V30M mutation.

4.(iii).A.(3).2) Japanese phase III study (5.3.5.2.3, Study B3461010 [November 2011 to ongoing (data cut-off date, February 19, 2013)])

An open-label, uncontrolled study was conducted in Japanese patients with TTR-FAP (Target sample size of 10) to determine the percent stabilization of TTR tetramer[5)] and evaluate the efficacy, safety, and pharmacokinetics of tafamidis [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics and the percent stabilization of TTR tetramer[5)]].

Tafamidis 20 mg/day was to be orally administered once daily.

All of 10 treated subjects (9 patients with the V30M mutation, 1 patient with the S77Y mutation) were included in the safety population and the FAS (Full Analysis Set) for efficacy analyses. No subjects in the safety population discontinued by Week 52.[45)]

The primary endpoint of the proportion of subjects with a TTR percent stabilization[5)] of >32%[37)] at Week 8 in the FAS was 100% (10 of 10 subjects). The secondary endpoints of NIS-LL and TQOL scores over time were as shown in Table 23.

Table 23. NIS-LL and TOQL scores over time

	NIS-LL	TQOL
Baseline	17.0 ± 13.1	52.9 ± 32.8
Week 26	19.1 ± 14.5	64.7 ± 39.0
Week 52	20.6 ± 14.7	62.0 ± 38.4

Mean ± SD
N = 10

The incidence of adverse events was 100% (10 of 10 subjects), but no death occurred by Week 52.[45)] Other serious adverse events occurred in 4 subjects (pneumonia bacterial [3 subjects], pyelonephritis and burns third degree [1 subject]), but a causal relationship to study drug was denied for all events.

An adverse event for which a causal relationship to study drug could not be denied was ingival swelling that occurred in 1 subject.

As to vital signs (blood pressure, pulse rate, body temperature, respiratory rate), an increase in systolic blood pressure of ≥30 mmHg (supine position) (3 subjects) and an increase in diastolic blood pressure of ≥20 mmHg (supine position) (4 subjects) at Week 26 and an increase in systolic blood pressure of ≥30 mmHg (supine position) (1 subject) and an increase in diastolic blood pressure of ≥20 mmHg (supine position) (2 subjects) at Week 52 were observed. New abnormal ECGs detected after the start of treatment were as shown in Table 19 and no new abnormal echocardiograms were detected after the start of treatment.

Based on the above, the applicant explained that the efficacy of tafamidis 20 mg/day has been suggested and there should be no major safety problem in Japanese patients with TTR-FAP.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of tafamidis

PMDA asked the applicant to explain the clinical positioning of tafamidis in the treatment of TTR-FAP.

45) Death due to completed suicide (1 subject) occurred at Month 15.

The applicant explained as follows:

The only therapy for TTR-FAP to delay peripheral neurologic impairment etc. in both Japan and overseas is orthotopic transplantation of the liver, where TTR is primarily synthesized (Ando Y, et al. *Rare/Intractable Disease Project supported by the Health and Labour Sciences Research Grant: Amyloidosis Research Committee [led by Yamada M.], 2010 Clinical Practice Guideline for Amyloidosis*. 2010;20-26, A physician's guide to transthyretin amyloidosis. http://www.amyloidosis.org/pdf/TTR%2008.pdf). There are problems with liver transplantation, e.g. the shortage of donor organs and the need for life-long immunosuppressant therapy even after liver transplantation. It has also been reported that approximately 20% of patients who had undergone liver transplantation also required assistance with ambulation due to continued deposition of amyloid derived from wild-type TTR and variant TTR produced by tissues other than the liver (Liepnieks JJ, et al. *Neurology*. 2010;75:324-327). Thus, no satisfactorily effective therapy has been established to date. Although some NSAIDs such as diflunisal have been identified as having a pharmacological activity similar to tafamidis (Baures PW, et al. *Bioorg Med Chem*. 1998;6:1389-1401, Baures PW, et al. *Bioorg Med Chem*. 1999;7:1339-1347), their efficacy and safety have not been demonstrated in clinical studies. Also, there are currently no guidelines that mention the clinical positioning of tafamidis in Japan or overseas. However, tafamidis that is considered to inhibit TTR amyloid formation by stabilizing tetrameric TTR [see "3.(i).B.(1) Mechanism of action of tafamidis"] has been shown to delay peripheral neurologic impairment in Japanese and foreign clinical studies, and the drug can be used also in patients on the liver transplantation list and patients who are not eligible for liver transplantation due to their age etc. Therefore, tafamidis offers a new option for the treatment of TTR-FAP.

Given that the only effective therapy for TTR-FAP is liver transplantation, PMDA considers that tafamidis will become a new option for the treatment of TTR-FAP.

4.(iii).B.(2) Efficacy of tafamidis

Taking into account that TTR-FAP is an ultra-rare disease, PMDA evaluated the efficacy of tafamidis based on the data from clinical studies submitted in the application, positioning a foreign phase II/III study in foreign patients with TTR-FAP (V30M patients) (5.3.5.1.1, Study Fx-005) as a pivotal efficacy study and a Japanese phase III study in Japanese patients with TTR-FAP (V30M and S77Y patients) (5.3.5.2.3, Study B3461010) as a clinical study to determine TTR stabilization and exploratorily evaluate the efficacy of tafamidis in slowing TTR-FAP progression in Japanese patients.

4.(iii).B.(2).1) Foreign phase II/III study (5.3.5.1.1, Study Fx-005)

4.(iii).B.(2).1).(a) Appropriateness of efficacy endpoints

PMDA asked the applicant to explain the appropriateness of selecting the percentage of NIS-LL responders[43)] and the change in the TQOL score as the co-primary efficacy endpoints for Study Fx-005 (5.3.5.1.1).

The applicant explained as follows:

There is no clinical assessment tool developed for TTR-FAP patients, nor has interventional clinical trial been

conducted in TTR-FAP. Thus, the use of an existing reliable and validated instrument capable of assessing the progression of peripheral neuropathy was considered as a measure of drug efficacy in TTR-FAP. Since (1) the NIS has been used widely in clinical trials assessing efficacy in patients with neuropathy (Laaksonen S. *Neurophysiologic diagnosis, clinical symptoms and neuropathologic findings in polyneuropathies.* Turun yliopiston julkaisuja annales universitatis turkuensis. 2009) and (2) the main feature of TTR-FAP is an axonal length-dependent neuropathy and the lower limbs are most affected in early-stage TTR-FAP, the NIS-LL was selected as an outcome measure so that the progression of the disease can be assessed and detected over time. Next, since an expert consensus report states that a 2-point difference in NIS-LL scores between treatment groups is clinically meaningful and is the least detectable change by a neurologist (Dyck PJ, et al. *Ann Neurol*. 1995;38:478-482), patients with an increase from baseline in NIS-LL of <2 points were categorized as responders and patients with an increase from baseline in NIS-LL of ≥2 points or patients who discontinued the study were categorized as non-responders, and thus the percentage of responders was selected as a primary endpoint. Furthermore, when the primary endpoint for Study Fx-005 (5.3.5.1.1) was discussed with a foreign regulatory authority, the regulatory authority pointed out that as the NIS-LL is a total score of assessments of different sites of the lower limbs that are of different clinical significance, the clinical significance of the NIS-LL is unclear. For this reason, TQOL score that is reliable and validated for patients with diabetic neuropathy was added as a primary endpoint and the percentage of NIS-LL responders[43)] and the change in the TQOL score were chosen as the co-primary endpoints. As the secondary endpoints, the composite score for large nerve fiber function (Σ7 NTs NDS)[46)] and the composite score for small nerve fiber function (Σ3 NTSF NDS)[47)] that can also assess autonomic function were chosen. The modified BMI (mBMI)[48)] that can assess general nutritional status in TTR-FAP patients was also used.

4.(iii).B.(2).1).(b) Efficacy in Study Fx-005 (5.3.5.1.1)

In Study Fx-005 (5.3.5.1.1) that was the only placebo-controlled, randomized, double-blind, parallel-group study of tafamidis, no statistically significant differences were observed between the tafamidis and placebo groups for both co-primary endpoints, the percentage of NIS-LL responders at Month 18 and the change from baseline to Month 18 in the TQOL score in the ITT population. PMDA asked the applicant to explain the cause of the results and the justification for interpreting that the efficacy of tafamidis has been shown in this study.

The applicant explained as follows:

At the time of designing Study Fx-005 (5.3.5.1.1), 3 to 6 dropouts were assumed per treatment group, but the actual number of dropouts in the ITT population was 34 (17 dropouts per treatment group) and especially, the study had a much higher dropout rate than anticipated because some patients discontinued the study due to liver transplant (13 dropouts per treatment group).The time of discontinuation was similar between the placebo

46) Composite score consisting of vibration detection threshold of the hallux, heart rate response to deep breathing, and 5 nerve conduction studies (peroneal nerve distal motor latency, peroneal nerve compound muscle action potential amplitude, peroneal nerve motor conduction velocity, tibial nerve distal motor latency, sural nerve sensory nerve action potential).

47) Composite score consisting of cooling threshold for the lower limbs, heat pain threshold for the lower limbs, and heart rate response to deep breathing.

48) The product of the BMI and serum albumin concentration. Edema and subsequent body weight increase may be caused by malnutrition associated with gastrointestinal dysfunction in TTR-FAP patients. Modified BMI can correct for the effects of edema on body weight and the mBMI was found to correlate closely with survival in TTR-FAP patients who had not undergone liver transplant.

and tafamidis groups, though its reason is unknown. A conservative statistical approach was used for the primary analysis of the co-primary efficacy endpoints; all patients who discontinued the study due to liver transplantation were categorized as "non-responders" in the analysis of the NIS-LL[43] and the last observation carried forward (LOCF) method was used to impute missing data in the analysis of TQOL scores. Thus, the applicant considered that a higher dropout rate reduced the power of the ITT analysis, resulting in no statistically significant differences. The percentage of NIS-LL responders[43] and the change from baseline in the TQOL score in the efficacy evaluable population (EE)[49] (42 subjects in the placebo group, 45 subjects in the tafamidis group), which was pre-specified in the statistical analysis plan, were as shown in Table 24 and Table 25, respectively, demonstrating statistically significant differences for both co-primary endpoints. In addition, a sensitivity analysis of the NIS-LL[43] was performed by changing the handling of patients who discontinued the study due to liver transplantation.[50] As a result, the percentage of NIS-LL responders[43] was 36.1% (22 of 61 subjects) in the placebo group and 54.7% (35 of 64 subjects) in the tafamidis group and the treatment difference and its 95% confidence interval were 18.6 [1.5, 35.8]%. A statistically significant difference was observed ($P = 0.0367$, chi-square test).

Table 24. Percentage of NIS-LL responders in Study Fx-005 (5.3.5.1.1) (EE)

	N	NIS-LL score		% of responders (No. of responders)	Treatment difference [95% CI]	*P*-value[a]
		Baseline	Month 18			
Placebo	42	12.0 ± 14.01	17.6 ± 20.08	38.1 (16)	21.9 [1.4, 42.4]	0.0411
Tafamidis	45	6.4 ± 9.64	8.39 ± 12.45	60.0 (27)		

Mean ± SD
a) Chi-square test

Table 25. Change in TQOL score in Study Fx-005 (5.3.5.1.1) (EE)

	N	TQOL score		Change[a]	Treatment difference [95% CI][b]	*P*-value[b]
		Baseline	Month 18			
Placebo	42	29.1 ± 28.28	36.8 ± 29.52	8.9 ± 3.1	-8.8 [-17.4, -0.2]	0.0454
Tafamidis	45	21.1 ± 20.86	22.4 ± 22.56	0.1 ± 3.0		

Mean ± SD
a) Least-squares mean ± SE
b) ANCOVA with treatment as a factor and baseline value as a covariate

The applicant presented the secondary endpoints (Σ7 NTs NDS,[46] Σ3 NTSF NDS,[47] mBMI[48]) over time in Study Fx-005 (5.3.5.1.1) (Table 26) and explained that the results of these endpoints also suggested the efficacy of tafamidis.

[49] The efficacy evaluable population was defined as patients who had NIS-LL and TQOL scores at Month 18, who took at least 80% of the prescribed study drug, and who had no major protocol violations. As a result, all patients who discontinued (34 patients) and patients with major protocol violations (4 patients: pregnancy [1 patient in the placebo group], medication error [1 patient in the tafamidis group], negative biopsy [1 patient each in the placebo and tafamidis groups]) were excluded from the ITT population.

[50] The NIS-LL response rate at Month 18 in non-liver transplant patients was modeled using logistic regression with treatment and baseline NIS-LL as covariates. The NIS-LL response rate in liver transplant patients was estimated by this model using the median baseline NIS-LL for liver transplant patients and then NIS-LL response/nonresponse were imputed for liver transplant patients.

Table 26. Changes in Σ7 NTs NDS, Σ3 NTSF NDS, and mBMI over time in Study Fx-005 (5.3.5.1.1) (ITT, OC)

		Baseline value and change		Treatment difference[a)] [95% CI]
		Placebo	Tafamidis	
Σ7 NTs NDS	Baseline score	8.72 ± 8.53 (61)	7.79 ± 9.06 (64)	
	Month 6	1.93 ± 3.85 (57)	0.58 ± 3.54 (60)	-1.353 [-2.706, 0.000]
	Month 12	2.96 ± 3.88 (50)	0.83 ± 3.96 (48)	-1.958 [-3.467, -0.448]
	Month 18	3.33 ± 5.00 (46)	1.16 ± 3.85 (48)	-1.649 [-3.411, 0.114]
Σ3 NTSF NDS	Baseline score	5.62 ± 4.09 (61)	5.51 ± 4.54 (64)	
	Month 6	0.72 ± 2.20 (57)	0.24 ± 1.68 (60)	-0.476 [-1.191, 0.239]
	Month 12	1.25 ± 2.01 (50)	0.38 ± 2.05 (48)	-0.929 [-1.696, -0.163]
	Month 18	1.49 ± 2.52 (46)	0.29 ± 2.13 (48)	-1.281 [-2.160, -0.401]
mBMI	Baseline value	1011.5 ± 212.9 (61)	1004.6 ± 165.2 (64)	
	Month 6	-29.8 ± 69.7 (56)	17.1 ± 68.4 (60)	47.6 [22.3, 72.9]
	Month 12	-30.8 ± 74.9 (50)	19.4 ± 71.8 (49)	50.2 [21.5, 78.8]
	Month 18	-32.7 ± 88.6 (46)	37.9 ± 73.7 (49)	73.1 [40.4, 105.8]

Mean ± SD (N)

a) Least-squares mean difference between the tafamidis and placebo groups estimated from a mixed-effects model with repeated measures that included treatment, month, and treatment-by-month interaction as fixed effects and subject as a random effect

PMDA asked the applicant to explain the possibility that an imbalance between the treatment groups regarding baseline NIS-LL and TQOL scores in both the ITT and EE populations[49)] in Study Fx-005 (5.3.5.1.1) may have affected the efficacy of tafamidis.

The applicant explained as follows:

Since blocked randomization was performed without using any balancing factor in Study Fx-005 (5.3.5.1.1), the applicant considered that the play of chance led to an imbalance between the placebo and tafamidis groups regarding baseline NIS-LL and TQOL scores. Baseline TQOL score was included as a covariate in the primary analysis (ANCOVA) and its effect was taken into account in the analyses presented in Table 21 and Table 25, which showed a statistically significant difference in the EE population.[49)] Based on a logistic regression analysis with the percentage of NIS-LL responders at Month 18 as the response variable,[51)] baseline NIS-LL was found to affect the percentage of NIS-LL responders at Month 18, and a subgroup analysis suggested a trend towards reduced effect in the subgroup of patients with lower baseline NIS-LL (<4.5) [see Table 32]. However, due to a higher dropout rate, NIS-LL changes from baseline were analyzed using a mixed-effects model with repeated measures (MMRM) adjusted for baseline NIS-LL (Table 27), which also showed a statistically significant difference. Therefore, the imbalance in baseline scores had no significant effect on the efficacy of tafamidis.

Table 27. NIS-LL change from baseline in Study Fx-005 (5.3.5.1.1) (ITT, MMRM)

	N	Baseline	Change[a)]	Treatment difference [95% CI][b)]	*P*-value
Placebo	61	11.4 ± 13.54	5.61 ± 0.92	-2.67 [-5.24, -0.09]	0.043
Tafamidis	64	8.4 ± 11.40	2.95 ± 0.91		

Mean ± SD

a) Least-squares mean ± SE

b) A mixed-effects model with repeated measures that included treatment, month, treatment-by-month interaction, and baseline NIS-LL as fixed effects and subject as a random effect

Since 58% of patients included in Study Fx-005 (5.3.5.1.1) were enrolled at one site in Portugal, PMDA asked the applicant to explain the consistency of the efficacy of tafamidis across the regions.

51) A logistic regression analysis with the NIS-LL response rate at Month 18 as the response variable, treatment, gender, and site as categorical covariates, and age, baseline NIS-LL, and duration of disease as continuous covariates.

The applicant explained as follows:

The clinical pictures of TTR-FAP patients with the V30M mutation in Japan, Portugal, and Sweden with endemic areas are as shown in Table 28. The age of onset tends to be earlier in Portugal, a primary endemic region overseas, and Kumamoto Prefecture and Nagano Prefecture in Japan as compared to Sweden and other areas in Japan and its onset is in old age in France, Italy, and the US as well.[52] Also in Study Fx-005 (5.3.5.1.1), subjects tended to be younger and the duration of disease tended to be shorter at one site in Portugal compared to other sites. Furthermore, the changes from baseline to Month 18 in the NIS-LL and TQOL scores at the site in Portugal and other sites are presented in Table 29 and these results showed a trend towards a greater treatment difference at the site in Portugal, though exploratory ones. The clinical picture of TTR-FAP patients varies among different endemic regions. Although the reason for differences in the clinical picture among different endemic regions in spite of the same genetic mutation is not clear at present, there should be no major differences in the pathology of the disease (TTR misfolding and aggregation cause neurodegeneration). Thus, taking into account the mechanism of action of tafamidis [see "3.(i).B.(1) Mechanism of action of tafamidis"], the efficacy of tafamidis can be expected, regardless of the clinical picture of patients, e.g. the age of onset.

Table 28. Clinical picture of TTR-FAP patients with V30M mutation

	Nagano Prefecture	Kumamoto Prefecture	Ishikawa Prefecture	Non-endemic areas in Japan	Portugal	Sweden
Mean age of onset (years)	33.8	35.6	62.9	62.7	33.5	53
Male to female ratio	1:1	1:1.1	1.2:1	10:1	1.9:1	2:1
Rate of family history	High rate	High rate	High rate	Low rate	High rate	High rate
Severity of autonomic neuropathy	Severe	Severe	Moderate	Mild	Severe	Severe
Mean age of death (years)	Unknown	46.6	70.0	Unknown	40.8	65.6
Mean years of diagnosis (years)	12-15	9.8	8.4	Unknown	10.6	12

Kato-Motozaki Y, et al. *J Neurol Sci*. 2008;270:133-140

Table 29. Changes from baseline in NIS-LL and TQOL scores by site in Study Fx-005 (5.3.5.1.1) (ITT, LOCF)

	Treatment group	N	NIS-LL score		TQOL score	
			Change	Treatment difference [95% CI][a)]	Change	Treatment difference [95% CI][a)]
One site in Portugal	Placebo	36	5.67 ± 8.76	-4.52 [-7.77, -1.26]	9.0 ± 20.59	-6.2 [-14.7, 2.2]
	Tafamidis	36	1.15 ± 4.12		2.8 ± 15.00	
Other sites	Placebo	25	4.79 ± 7.72	-0.47 [-4.06, 3.13]	3.8 ± 26.00	-2.0 [-13.3, 9.4]
	Tafamidis	28	4.32 ± 4.11		1.8 ± 14.22	

Mean ± SD

a) Two-sided 95% confidence interval calculated using t distribution

4.(iii).B.(2).1).(c) Details of regulatory review in the US

PMDA asked the applicant to explain the reason for the FDA's decision not to approve tafamidis.

The applicant explained as follows:

In the course of regulatory review in the US, the FDA concluded, for the following reasons, that a foreign phase II/III study (5.3.5.1.1, Study Fx-005) is not [redacted] and the efficacy of tafamidis cannot be explained appropriately based only on the results from this study, and additional clinical study data

[52] Planté-Boordeneuve V, et al. *Neurology*. 1998;51:708-714, Planté-Boordeneuve V, et al. *Neurology*. 2007;69: 693-698, Di Iorio G, et al. *Ital J Neurol Sci*. 1993;14:303-309, Gertz MA, et al. *Mayo Clinic Proc*. 1992;67:428-440, Kim DH, et al. *Muscle Nerve*. 2009;40:363-370.

[redacted] need to be submitted.

i) [redacted]

ii) [redacted]

iii) [redacted]

iv) [redacted]

v) [redacted], the US FDA [redacted]

- [redacted]
- [redacted]

Then, the applicant explained as follows:

Regarding the items i) to iii) listed above, as described in "4.(iii).B.(2).1).(b) Efficacy in Study Fx-005 (5.3.5.1.1)", the results from Study Fx-005 (5.3.5.1.1) suggested the efficacy of tafamidis. As to v), discussion on [redacted] with the FDA is currently ongoing.

PMDA considers as follows:

When interpreting the results from Study Fx-005 (5.3.5.1.1), it should be noted that in spite of the random allocation of treatments to subjects, there was an imbalance between the treatment groups regarding the baseline disease characteristics of patients such as baseline NIS-LL and TQOL scores. Meanwhile, the results of analyses adjusted for the baseline values indicate that the effect of the imbalance is not great enough to make the interpretation of the study results difficult. Although the results of Study Fx-005 (5.3.5.1.1) mostly reflect patients at one site in Portugal, given that TTR-FAP is an ultra-rare disease and that the pathogenesis of the disease is common across different endemic regions, discussing the efficacy of tafamidis based on the results from this study is acceptable. While Study Fx-005 (5.3.5.1.1) failed to confirm the superiority of

tafamidis over placebo, multiple sensitivity analyses of the NIS-LL and TQOL scores and analyses of the secondary endpoints such as the percent stabilization of TTR tetramer[5)] suggested the efficacy of tafamidis, though exploratory ones.

4.(iii).B.(2).2) Japanese phase III study (5.3.5.2.3, Study B3461010)

PMDA asked the applicant to explain the appropriateness of selecting the proportion of subjects with a TTR percent stabilization[5)] of >32%[37)] at Week 8 as the primary endpoint for a Japanese phase III study (5.3.5.2.3, Study B3461010).

The applicant explained as follows:

In a foreign phase II/III study (5.3.5.1.1, Study Fx-005), a logistic regression analysis with the percentage of NIS-LL responders[43)] at Month 18 as the response variable and the percent stabilization of TTR tetramer[5)] at Week 8 (≤32%[37)] or >32%) as the explanatory variable was conducted. As a result, the odds ratio for the percent stabilization of TTR tetramer[5)] at Week 8 was 2.054 (P = 0.0738) and the percent stabilization of TTR tetramer[5)] at Week 8 was considered to be a predictor of the clinical benefit of tafamidis in slowing disease progression. When Pfizer Inc. gained the license to tafamidis through the acquisition of FoldRx (the US), the foreign phase II/III study (5.3.5.1.1, Study Fx-005) had already been completed, which means that it was impossible for patients in Japan to participate in the study. Since the number of TTR-FAP patients in Japan is limited, around 111 to 140 (Motozaki Y, et al. *Journal of Clinical and Experimental Medicine*. 2009;229:357-362, Kato-Motozaki Y, et al. *J Neurol Sci*. 2008;270:133-140) and it was considered difficult to conduct a placebo-controlled study in Japan alone, TTR stabilization[5)] at Week 8 was chosen as the primary endpoint for a Japanese study and the clinical outcome measures of the NIS-LL, TQOL, etc. at both Weeks 26 and 52 were also used for reference for the comparison with the foreign phase II/III study, and thereby the efficacy of tafamidis in Japanese TTR-FAP patients was evaluated (5.3.5.1.1, Study Fx-005).

The proportions of subjects with a TTR percent stabilization[5)] of >32%[37)] in Study B3461010 (5.3.5.2.3) and Study Fx-005 (5.3.5.1.1) were as shown in Table 14 and Table 15, respectively. The percent stabilization of TTR tetramer[5)] was increased also in Japanese TTR-FAP patients and there were no major differences between the two studies. The NIS-LL and TQOL changes from baseline to Week 52/Month 12 in the two studies (Table 30) were compared, which showed a trend towards greater changes in the NIS-LL and TQOL scores with tafamidis in Study B3461010 (5.3.5.2.3). However, the study outcomes may have been affected by some subjects with marked increases in the TQOL score at Week 52 and analyses excluding these subjects showed no major differences in the NIS-LL and TQOL scores between the two studies. Therefore, there should be no major differences in the changes in the NIS-LL and TQOL scores between Study B3461010 (5.3.5.2.3) and Study Fx-005 (5.3.5.1.1).

Table 30. Changes in NIS-LL and TQOL scores in Study B3461010 and Study Fx-005 (LOCF)

		Study B3461010[a] (5.3.5.2.3)	Study Fx-005[b] (5.3.5.1.1)	
			Placebo	Tafamidis
N		10	61	64
NIS-LL score	Baseline	17.0 ± 13.1	11.4 ± 13.5	8.4 ± 11.4
	Change	3.6 ± 4.4	4.5 ± 7.3	1.3 ± 3.9
NIS-LL (muscle weakness) score	Baseline	10.1 ± 9.4	4.2 ± 9.3	2.9 ± 7.4
	Change	2.7 ± 3.5	2.4 ± 5.7	0.2 ± 2.4
NIS-LL (reflexes) score	Baseline	2.4 ± 1.4	1.7 ± 2.2	1.2 ± 2.0
	Change	0.3 ± 0.7	0.7 ± 1.2	0.5 ± 1.0
NIS-LL (sensation) score	Baseline	4.5 ± 3.0	5.6 ± 3.8	4.3 ± 3.4
	Change	0.7 ± 1.1	1.4 ± 2.3	0.7 ± 2.5
TQOL score	Baseline	52.9 ± 32.8	30.8 ± 26.7	27.3 ± 24.2
	Change	9.1 ± 12.5	4.4 ± 18.8	1.4 ± 14.5

Mean ± SD
a) FAS, Week 52, b) ITT, Month 12

Due to the limitations of efficacy assessment based on the NIS-LL and TQOL scores in the Japanese phase III study (5.3.5.2.3, Study B3461010), PMDA asked the applicant to explain the appropriateness of the use of foreign data for reference in order to discuss efficacy in Japanese patients, taking account of differences in the medical environment, the pathology of TTR-FAP, etc. between Japan and overseas.

The applicant explained as follows:
In both Japan and overseas, the current pharmacotherapies for TTR-FAP are aimed at symptomatic relief only and the only therapy for TTR-FAP to slow disease progression is orthotopic liver transplantation (Ando Y, et al. *Rare/Intractable Disease Project supported by the Health and Labour Sciences Research Grants: Amyloidosis Research Committee [led by Yamada M.], 2010 Clinical Practice Guideline for Amyloidosis*. 2010;20-26, A physician's guide to transthyretin amyloidosis. http://www.amyloidosis.org/pdf/TTR%2008.pdf) and there should be no major differences in the medical environment between Japan and overseas. With respect to liver transplantation, deceased donor transplantation is the mainstay of liver transplantation in Europe/the US while living donor liver transplantation is the mainstay in Japan (United Network for Organ Sharing, http://www.unos/org/, Adam R, et al. *J Hepatol*. 2012;57: 675-688, Japanese Liver Transplantation Society. *Japanese Journal of transplantation*. 2011;46:524-536). The annual number of liver transplants itself is small in Japan compared to Europe/the US. Meanwhile, the situation of the shortage of donor organs is similar. The time from TTR-FAP diagnosis to liver transplant is about 3 years in both Japan and overseas (Wilczek HE, et al. *Amyloid*. 2011;18:193-195, Takei Y, et al. *Internal Med*. 2005;44:1151-1156) and the timing of transplantation is also similar between Japan and overseas.

A comparison of the baseline demographics and disease characteristics of patients between Study B3461010 (5.3.5.2.3) and Study Fx-005 (5.3.5.1.1) is shown in Table 31. There was a trend towards differences in all items excluding gender between the two studies and the baseline demographics and disease characteristics of TTR-FAP patients enrolled into Study B3461010 (5.3.5.2.3) (Table 31) tended to be different also from the clinical picture of TTR-FAP patients with the V30M mutation in Nagano Prefecture and Kumamoto prefecture where this study was conducted (Table 28). In Japan, liver transplantation is considered for a TTR-FAP patient if (i) the duration of disease is ≤5 years and the patient is able to perform activities of daily living independently, (ii) the patient has no major dysfunction of the heart and kidney and is in good general conditions, and (iii) the age is ≤60 years (Ikeda S. *Clinical Neurology*. 2009;49:953-955). Taking account of the seriousness of the

disease, Study B3461010 (5.3.5.2.3) mainly enrolled patients who were not eligible for liver transplantation as the current standard therapy and patients to whom transplantation was not readily available. Consequently, the study population was different from a representative patient population in these areas.

Table 31. Baseline demographics and disease characteristics of patients in Study B3461010 and Study Fx-005

		Study B3461010[a] (5.3.5.2.3)	Study Fx-005[b] (5.3.5.1.1)	
			Placebo	Tafamidis
N		10	61	64
Gender[c]	Male	70.0 (7)	42.6 (26)	50.0 (32)
	Female	30.0 (3)	57.4 (35)	50.0 (32)
Age (years)		60.1 ± 13.0	38.4 ± 12.9	39.8 ± 12.7
Age of onset (years)		58.4 ± 13.1	36.0 ± 11.5	36.3 ± 10.8
Duration of disease (years)		1.9 ± 2.4	2.9 ± 2.7	3.9 ± 4.0
NIS-LL score		17.0 ± 13.1	11.4 ± 13.5	8.4 ± 11.4
TQOL score		52.9 ± 32.8	30.8 ± 26.7	27.3 ± 24.2

Mean ± SD
a) FAS, b) ITT
c) % (n)

Although the baseline demographics and disease characteristics of enrolled patients in Study B3461010 (5.3.5.2.3) and Study Fx-005 (5.3.5.1.1) and the typical clinical picture of TTR-FAP patients in Japan tended to differ from one another, even if the genetic mutation or clinical picture is different, there should be no major differences in the main pathology of the disease (TTR misfolding and aggregation cause axonal length-dependent neurodegeneration leading to autonomic, sensory, and motor impairment).

Based on the above, there are no differences in the pathology of TTR-FAP or the medical environment between Japan and overseas that would affect the efficacy assessment of tafamidis and in addition to Japanese clinical study data, foreign data can be used for reference to be compared to the Japanese data for the evaluation of the efficacy of tafamidis in Japanese TTR-FAP patients.

PMDA considers as follows:
The target disease of tafamidis, TTR-FAP, is an ultra-rare disease. Although differences in the pathology of TTR-FAP between regions are not necessarily defined, the current findings suggest a common pathogenesis. There are no major differences in the medical environment between Japan and overseas. In light of these points, it is possible to discuss the efficacy of tafamidis in Japanese patients, by referring to Study Fx-005 (5.3.5.1.1) in addition to Study B3461010 (5.3.5.2.3), which was conducted as an open-label, uncontrolled study. As the baseline demographics and disease characteristics of TTR-FAP patients in Study B3461010 (5.3.5.2.3) were slightly different from those in Study Fx-005 (5.3.5.1.1) and the limited number of patients were studied, it is difficult to adequately compare the clinical endpoints such as the NIS-LL and TQOL scores over time between Study B3461010 (5.3.5.2.3) and Study Fx-005 (5.3.5.1.1). However, taking into account the demonstration of TTR stabilization at Week 8 and the mechanism of action of tafamidis, a certain level of efficacy of tafamidis can be expected also in Japanese TTR-FAP patients.

4.(iii).B.(2).3) Efficacy of tafamidis

PMDA considers as follows:

Based on the above 1) and 2), although the efficacy of tafamidis has not been confirmed in Japanese and foreign clinical studies, the results from Study Fx-005 (5.3.5.1.1) have suggested the efficacy of tafamidis and the results from Study B3461010 (5.3.5.2.3) indicate that a certain level of efficacy of tafamidis can be expected also in Japanese TTR-FAP patients. Given that TTR-FAP is an ultra-rare, fatal disease for which the only effective therapy is liver transplantation, tafamidis can be offered to medical practice in Japan, based on these study results. Since no definitive conclusion on the efficacy of tafamidis can be derived from Study Fx-005 (5.3.5.1.1), it is necessary to continue to collect information on the clinical outcome and prognosis of TTR-FAP patients treated with tafamidis globally and collect a highest possible level of evidence for the effect of tafamidis in delaying peripheral neurologic impairment. As the Transthyretin Amyloidosis Outcome Survey (THAOS)[53] is currently ongoing overseas and some medical institutions in Japan are also participating in the survey in which patients have been enrolled in the registry, it is important that such study results will appropriately be provided to medical practice in Japan. Since clinical experience and efficacy assessment in Japanese patients in Study B3461010 (5.3.5.2.3) are limited, it is necessary to continue to evaluate the efficacy of tafamidis using clinical outcome measures via post-marketing surveillance in Japan. It is also necessary to collect information on the long-term prognosis of Japanese patients wherever possible so as to help explain the clinical significance of tafamidis.

The appropriateness of the above conclusions will be determined, taking account of comments from the Expert Discussion.

4.(iii).B.(2).4) Factors affecting the efficacy of tafamidis

PMDA asked the applicant to explain the factors potentially affecting the efficacy of tafamidis.

The applicant presented the changes from baseline in the NIS-LL and TQOL scores by baseline demographics and disease characteristics of patients in a foreign phase II/III study (5.3.5.1.1, Study Fx-005) (Table 32) and explained that the treatment difference in the NIS-LL change from baseline tended to be smaller in the subgroup of patients with baseline NIS-LL less than the median [see "4.(iii).B.(2).1).(b) Efficacy in Study Fx-005 (5.3.5.1.1)" for details]. The applicant also explained that the treatment difference in the TQOL change from baseline tended to be smaller in the subgroup of patients with baseline NIS-LL equal to or higher than the median, which was considered associated with several placebo-treated subjects in this subgroup showing marked improvement in the TQOL score of ≥20 points during the treatment period.

[53] An investigator-initiated, disease registry for TTR amyloidosis, which was established in 2007.

Table 32. NIS-LL and TQOL scores by baseline demographics and disease characteristics of patients in Study Fx-005 (5.3.5.1.1) (ITT, LOCF)

		Treatment group	N[b)]	NIS-LL score		TQOL score	
				Change	Treatment difference [95% CI][c)]	Change	Treatment difference [95% CI][c)]
Gender	Male	Placebo	25	7.3 ± 8.9	-3.34 [-7.03, 0.36]	9.1 ± 27.8	-6.60 [-18.12, 4.92]
		Tafamidis	29	4.0 ± 4.0		2.5 ± 12.6	
	Female	Placebo	32	3.8 ± 7.6	-2.74 [-5.87, 0.38]	5.1 ± 20.2	-2.90 [-12.38, 6.58]
		Tafamidis	31	1.0 ± 4.3		2.2 ± 17.3	
Body weight	<62.4 kg[a)]	Placebo	25	4.4 ± 7.3	-1.69 [-4.89, 1.52]	8.1 ± 26.6	-5.20 [-16.75, 6.35]
		Tafamidis	33	2.8 ± 4.8		2.9 ± 17.3	
	≥62.4 kg[a)]	Placebo	32	6.1 ± 9.1	-3.92 [-7.68, -0.17]	5.9 ± 21.6	-4.20 [-13.56, 5.17]
		Tafamidis	27	2.1 ± 3.8		1.7 ± 12.1	
Age of onset	<50 years	Placebo	47	4.8 ± 8.3	-2.68 [-5.33, -0.03]	6.0 ± 24.2	-3.97 [-11.92, 4.08]
		Tafamidis	49	2.1 ± 4.2		2.1 ± 14.3	
	≥50 years	Placebo	10	7.9 ± 8.5	-3.85 [-10.11, 2.40]	10.9 ± 22.1	-7.35 [-26.07, 11.36]
		Tafamidis	11	4.1 ± 4.8		3.6 ± 18.8	
Duration of disease	<1.8 years[a)]	Placebo	31	4.2 ± 8.4	-3.09 [-6.47, 0.28]	8.4 ± 12.8	-8.71 [-14.37, -3.04]
		Tafamidis	28	1.1 ± 3.1		-0.3 ± 8.1	
	≥1.8 years[a)]	Placebo	26	6.7 ± 8.2	-3.05 [-6.54, 0.45]	5.0 ± 32.5	-0.35 [-14.05, 13.35]
		Tafamidis	32	3.7 ± 5.0		4.7 ± 19.0	
Blood TTR concentration	<22.8 mg/dL[a)]	Placebo	26	5.7 ± 8.0	-3.69 [-7.01, -0.37]	7.3 ± 28.3	-2.36 [-13.85, 9.12]
		Tafamidis	32	2.0 ± 4.5		4.9 ± 14.4	
	≥22.8 mg/dL[a)]	Placebo	31	5.0 ± 8.7	-2.01 [-5.74, 1.71]	6.6 ± 19.5	-7.51 [-16.92, 1.90]
		Tafamidis	27	3.0 ± 4.4		-1.0 ± 15.7	
Baseline NIS-LL	<4.5[a)]	Placebo	24	2.2 ± 2.9	0.27 [-1.56, 2.10]	8.3 ± 13.7	-8.79 [-16.15, -1.43]
		Tafamidis	35	2.5 ± 3.8		-0.5 ± 14.0	
	≥4.5[a)]	Placebo	33	7.6 ± 10.1	-5.15 [-9.59, -0.70]	5.8 ± 29.1	0.50 [-12.41, 13.42]
		Tafamidis	25	2.5 ± 5.2		6.3 ± 15.8	
Baseline TQOL	<21[a)]	Placebo	28	3.1 ± 8.5	-1.77 [-4.89, 1.36]	10.4 ± 17.9	-5.33 [-13.24, 2.58]
		Tafamidis	34	1.3 ± 3.0		5.0 ± 13.2	
	≥21[a)]	Placebo	29	7.5 ± 7.7	-3.55 [-7.18, 0.08]	3.5 ± 28.1	-4.63 [-17.34, 8.08]
		Tafamidis	26	4.0 ± 5.4		-1.1 ± 16.8	

Mean ± SD
a) Median
b) Subjects with efficacy assessments at baseline only were excluded.
c) Two-sided 95% confidence interval calculated using t distribution

PMDA considers as follows:

Since the possibility that baseline NIS-LL affects the efficacy of tafamidis cannot be ruled out and there was an imbalance between the treatment groups, care should be taken when interpreting the results. Meanwhile, based on the results of a sensitivity analysis (Table 27) etc., the effect of the baseline value is not great enough to interfere with efficacy assessment. However, as there is limited clinical experience with tafamidis, it is necessary to continue to investigate the effect of baseline NIS-LL on the efficacy of tafamidis and continue to collect information on other factors as well via post-marketing surveillance.

4.(iii).B.(3) Safety of tafamidis

4.(iii).B.(3).1) Infections

PMDA asked the applicant to explain the occurrence of infections in Japanese and foreign clinical studies.

The applicant explained as follows:

Among adverse events related to infections[54)] in Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010), the incidences of the main events are presented in Table 33. In Study Fx-005 (5.3.5.1.1), the incidence of urinary tract infection tended to be higher in the tafamidis group than in the placebo group and serious events were also reported by 0 subjects in the placebo

54) Events in the MedDRA SOC "infections and infestations"

group and 2 subjects in the tafamidis group. Although the incidence tended to be higher in the subgroup of patients with bladder and rectal disturbance[55] (15.8% in the placebo group and 27.5% in the tafamidis group among the subgroup of patients with bladder and rectal disturbance,[55] 8.0% in the placebo group and 16.0% in the tafamidis group among the subgroup of patients without bladder and rectal disturbance), the trend of occurrence by the presence or absence of bladder and rectal disturbance[55] was similar between the placebo and tafamidis groups, for which the details are unknown at present. Therefore, an investigation to find the reason for this finding will be continued via post-marketing surveillance. In Study B3461010 (5.3.5.2.3), bacterial pneumonia occurred in 3 subjects, which were all serious events. All of these events were likely to be caused by dysphagia associated with the primary disease and their causal relationship to tafamidis was denied. Furthermore, in Study Fx-005 (5.3.5.1.1), the incidences of vaginal infection among women were 2.7% (1 of 37 subjects) in the placebo group and 12.1% (4 of 33 subjects) in the tafamidis group.

Table 33. Incidences of main adverse events related to infections

	Study B3461010 (5.3.5.2.3)	Study Fx-005 (5.3.5.1.1)		Study Fx1A-201 (5.3.5.2.2)
		Placebo	Tafamidis	
N	10	63	65	21
Adverse events related to infections	80.0 (8)	52.4 (33)	66.2 (43)	38.1 (8)
Urinary tract infection	0	12.7 (8)	23.1 (15)	0
Influenza	10.0 (1)	14.3 (9)	15.4 (10)	4.8 (1)
Nasopharyngitis	30.0 (3)	12.7 (8)	13.8 (9)	4.8 (1)
Upper respiratory tract infection	0	4.8 (3)	6.2 (4)	4.8 (1)
Pharyngitis	0	7.9 (5)	6.2 (4)	0
Vaginal infection	0	1.6 (1)	6.2 (4)	0
Sinusitis	0	0	3.1 (2)	9.5 (2)
Rhinitis	0	4.8 (3)	3.1 (2)	0
Tonsillitis	0	3.2 (2)	3.1 (2)	0
Vulvovaginal candidiasis	0	1.6 (1)	3.1 (2)	0
Viral infection	0	0	3.1 (2)	0
Bacterial pneumonia	30.0 (3)	0	0	0

Incidence (%) (n)

PMDA asked the applicant to explain the potential for tafamidis to affect the immune function or cause hematologic disorder.

The applicant explained as follows:

Changes in immune system-related laboratory parameters in Study Fx-005 (5.3.5.1.1) are presented in Table 34. No treatment-related effects were observed and there were also no major changes in other laboratory parameters related to hematologic disorder. The incidences of abnormalities in immune system-related laboratory parameters in Study Fx-005 (5.3.5.1.1) are presented in Table 35. There was no trend towards a higher incidence in the tafamidis group. Furthermore, there was no clear trend towards a higher incidence of adverse events related to infections[54] in patients with low white blood cell count, lymphocyte count, or eosinophil count.

[55] Events in the MedDRA PTs: constipation; diarrhoea; abdominal pain; irritable bowel syndrome; dysuria; pollakiuria; nocturia; micturition urgency; urinary incontinence; and urinary retention.

Table 34. Changes in immune system-related laboratory parameters in Study Fx-005 (5.3.5.1.1)

	Placebo		Tafamidis	
	Baseline value	Change at Month 18	Baseline value	Change at Month 18
N	61	51	63	51
White blood cell count	7.31 ± 2.18	0.01 ± 2.38	7.36 ± 1.80	0.04 ± 1.33
Lymphocyte count	2.09 ± 0.53	-0.23 ± 0.52	2.12 ± 0.63	-0.08 ± 0.60
Neutrophil count	4.60 ± 1.78	0.30 ± 2.23	4.65 ± 1.57	0.14 ± 1.16
Basophil count	0.064 ± 0.037	-0.0112 ± 0.041	0.062 ± 0.026	-0.0039 ± 0.046
Eosinophil count	0.21 ± 0.14	-0.037 ± 0.13	0.16 ± 0.089	-0.022 ± 0.07
Monocyte count	0.35 ± 0.11	-0.009 ± 0.14	0.36 ± 0.12	0.004 ± 0.13

Mean ± SD ($\times 10^3/mm^3$)

Table 35. Incidences of abnormalities in immune system-related laboratory parameters in Study Fx-005 (5.3.5.1.1)

		Placebo		Tafamidis	
		Baseline	On-treatment	Baseline	On-treatment
N		61	62	63	65
White blood cell count	High	0	1.6 (1)	0	0
	Low	0	0	0	1.5 (1)
Lymphocyte count	Low	0	3.2 (2)	0	7.7 (5)
Neutrophil count	High	0	1.6 (1)	0	0
	Low	1.6 (1)	0	0	1.5 (1)

Incidence (%) (n)

PMDA considers as follows:

Taking account of the following points: (a) although no abnormalities in immune system-related laboratory parameters were observed in a clinical study, the incidences of urinary tract infection and vaginal infection were increased in the tafamidis group and serious events also occurred in some patients in Study Fx-005 (5.3.5.1.1); (b) though a causal relationship was denied, bacterial pneumonia and pyelonephritis were reported as serious adverse events in Study B3461010 (5.3.5.2.3); and (c) tafamidis may be expected to be used in post-liver transplant patients [see "4.(iii).B.(4).3) Post-liver transplant patients"], clinicians should be alerted adequately to the risk of infections associated with tafamidis and then the risk of infections should continue to be investigated via post-marketing surveillance.

4.(iii).B.(3).2) Gastrointestinal symptoms

PMDA asked the applicant to explain the occurrence of gastrointestinal symptoms in Japanese and foreign clinical studies.

The applicant explained as follows:

Among adverse events related to gastrointestinal symptoms[56] in Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010), the incidences of the main events are presented in Table 36. There was no trend towards a higher overall incidence in the tafamidis group, but the incidences of diarrhoea and abdominal pain upper tended to be higher with tafamidis. There was also no trend towards differences in the occurrence of adverse events related to gastrointestinal symptoms[56] among different ethnic groups or different mutations.

[56] Events in the MedDRA SOC "gastrointestinal disorders"

Table 36. Incidences of main adverse events related to gastrointestinal symptoms

	Study B3461010 (5.3.5.2.3)	Study Fx-005 (5.3.5.1.1)		Study Fx1A-201 (5.3.5.2.2)
		Placebo	Tafamidis	
N	10	63	65	21
Adverse events related to gastrointestinal symptoms	30.0 (3)	61.9 (39)	53.8 (35)	33.3 (7)
Diarrhoea	10.0 (1)	17.5 (11)	26.2 (17)	23.8 (5)
Nausea	20.0 (2)	12.7 (8)	12.3 (8)	9.5 (2)
Abdominal pain upper	0	3.2 (2)	12.3 (8)	0
Vomiting	20.0 (2)	12.7 (8)	10.8 (7)	14.3 (3)
Constipation	0	11.1 (7)	6.2 (4)	14.3 (3)
Abdominal pain	0	7.9 (5)	4.6 (3)	0
Gastrointestinal motility disorder	0	4.8 (3)	4.6 (3)	0

Incidence (%) (n)

Then, the applicant explained the possible reason for a trend towards a higher incidence of diarrhoea as follows: Loose stool observed in dogs in non-clinical studies was considered of little toxicological significance and as there was a trend towards higher risk in the subgroup of patients with bladder and rectal disturbance[55)] in Study Fx-005 (5.3.5.1.1) (15.8% in the placebo group and 35.0% in the tafamidis group among the subgroup of patients with bladder and rectal disturbance[55)], 20.0% in the placebo group and 12.0% in the tafamidis group among the subgroup of patients without bladder and rectal disturbance), autonomic dysfunction may be one of the risk factors, but the details are unknown at present.

Furthermore, among subjects with diarrhoea, 1 subject had concurrent malnutrition, but no subjects had concurrent dehydration etc. One subject died due to ileus in a foreign long-term extension study (Reference data, 5.3.5.2.4, Study Fx1A-303), but its causal relationship to tafamidis was denied. As many of subjects with abdominal pain upper had concurrent constipation or diarrhoea, it is considered that abdominal pain upper was associated with constipation or diarrhoea.

PMDA considers as follows:
Based on the currently presented data, diarrhoea associated with tafamidis is unlikely to become a clinically significant problem, but it is necessary to continue to collect information via post-marketing surveillance.

4.(iii).B.(3).3) Central nervous system adverse events

PMDA asked the applicant to explain the occurrence of central nervous system adverse events in Japanese and foreign clinical studies.

The applicant explained as follows:
Among central nervous system adverse events[57)] in Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010), the incidences of the main events are presented in Table 37. No increased risk was observed in the tafamidis group compared to the placebo group and there were no ethnic differences in the occurrence of central nervous system adverse events or no trend towards differences among different mutations.

[57)] Events in the MedDRA SOCs “nervous system disorders” and “psychiatric disorders”

Table 37. Incidences of main central nervous system adverse events

	Study B3461010 (5.3.5.2.3)	Study Fx-005 (5.3.5.1.1)		Study Fx1A-201 (5.3.5.2.2)
		Placebo	Tafamidis	
N	10	63	65	21
Central nervous system adverse events	30.0 (3)	61.9 (39)	43.1 (28)	38.1 (8)
Headache	10.0 (1)	19.0 (12)	15.4 (10)	4.8 (1)
Anxiety	0	4.8 (3)	6.2 (4)	0
Depression	0	4.8 (3)	6.2 (4)	0
Paraesthesia	0	15.9 (10)	4.6 (3)	9.5 (2)
Somnolence	0	1.6 (1)	4.6 (3)	0
Neuralgia	0	19.0 (12)	3.1 (2)	9.5 (2)
Dizziness	0	6.3 (4)	3.1 (2)	14.3 (3)
Insomnia	10.0 (1)	3.2 (2)	3.1 (2)	0
Tension headache	0	0	3.1 (2)	0

Incidence (%) (n)

One subject on treatment with tafamidis died due to suicide[45)] in Study B3461010 (5.3.5.2.3). PMDA asked the applicant to explain the risk of suicide-related events associated with tafamidis.

The applicant explained as follows:

As to the suicide case in Study B3461010 (5.3.5.2.3), the subject had concurrent insomnia and anxiety and was taking etizolam. The cause of suicide was considered to be the suffering due to TTR-FAP and its causal relationship to study drug was denied. Moreover, based on clinical studies of tafamidis and the post-marketing safety information (November 16, 2011 to November 15, 2012, the estimated total exposure, 165 patient-years), no other suicides during treatment with tafamidis have been reported. Based on the above, tafamidis does not increase the risk of suicide-related events.

PMDA considers as follows:

Central nervous system adverse events are unlikely to become a clinically significant problem. Based on the currently available information, it is unnecessary to specifically caution about the risk of suicide-related events. However, as there is limited clinical experience with tafamidis in clinical studies and during marketing, it is necessary to continue to collect information via post-marketing surveillance and take appropriate safety measures as needed if a new finding becomes available.

4.(iii).B.(4) Indication for tafamidis

4.(iii).B.(4).1) Patients with non-V30M mutations

As a placebo-controlled, randomized, double-blind, parallel-group study of tafamidis was conducted in patients with the V30M mutation only, PMDA asked the applicant to explain the efficacy and safety of tafamidis in patients with other genetic mutations.

The applicant explained as follows:

Although >100 TTR mutations associated with TTR-FAP have been reported, the most common variant in Japan and overseas is V30M and accounts for 85% of TTR-FAP patients (Saraiva MJ, et al. *Hum Mutat*. 2001;17:493-503) and most of non-V30M mutations were reported from isolated patients or single families. While there are some variations in the clinical picture of TTR-FAP according to TTR mutation (Rapezzi C, et

al. *Amyloid*. 2006;13:143-153), there should be no major differences in the pathology of the disease, i.e. TTR misfolding and aggregation cause axonal length-dependent neurodegeneration leading to autonomic, sensory, and motor impairment. Tafamidis has been shown to inhibit the dissociation of non-V30M variants of TTR as well *in vitro* [see "3.(i).B.(1) Mechanism of action of tafamidis"]. As it was considered difficult to evaluate the efficacy and safety of tafamidis in TTR-FAP patients across all non-V30M TTR variants in clinical studies, the applicant planned to evaluate the efficacy and safety of tafamidis in patients with non-V30M mutations in a single, open-label, uncontrolled study (5.3.5.2.2, Study Fx1A-201). Though conducted in a small number of patients in an exploratory manner, Study Fx1A-201 (5.3.5.2.2) showed that the percent stabilization of TTR tetramer[5)] at Week 6 and the NIS-LL and TQOL changes from baseline to Month 12 varied widely regardless of genetic mutation. However, there was no trend towards marked differences in efficacy, and these study results did not tend to substantially differ from the results from Study Fx-005 (5.3.5.1.1) (Table 38). In Study Fx1A-201 (5.3.5.2.2), the NIS-LL and TQOL monthly rates of changes (0.39/month and 0.045/month, respectively) during the treatment period were slower than those before treatment (1.16/month and 1.044/month, respectively). In a Japanese patient with the S77Y mutation enrolled into Study B3461010 (5.3.5.2.3), the percent stabilization of TTR tetramer[5)] at Week 8 was 352.5% while the NIS-LL and TQOL scores worsened by 10.4 points and 26 points, respectively, at Week 52. These were the results of only 1 patient and it is difficult to derive a definitive conclusion on the efficacy of tafamidis in Japanese patients with this mutation from these results alone.

Table 38. Percent stabilization of TTR tetramer at Week 6 and NIS-LL and TQOL changes from baseline to Month 12 by TTR mutation

	TTR mutation	N	Percent stabilization of TTR tetramer[a)] at Week 6 (%)	NIS-LL change at Month 12	TQOL change at Month 12
Study Fx1A-201 (5.3.5.2.2)	L58H	3	353.1 ± 59.7	2.67 ± 6.53	-13.3 ± 10.2
	F64L	4	290.1 ± 69.5	2.97 ± 4.61	3.3 ±22.5
	T60A	3	266.0 ± 16.6	-0.17 ± 9.82	-3.0 ± 34.2
	G47A	3	236.1 ± 192.8	0.50 ± 0.71	-6.7 ± 7.6
	I107V	2	88.6, 281.4	-2.4, 11.5	3, 19
	S77Y	2	56.1, 347.9	2.0, 11.0	-3, 1
	D38A	1	198.7	-	-
	S77F	1	358.7	-4.0	21
Study Fx-005 (5.3.5.1.1)	V30M	61	179.9 ± 65.4	1.42 ± 3.93	1.2 ± 15.0

Mean ± SD, Individual values are listed for N ≤2.
a) Data at Week 8 for Study Fx-005 (5.3.5.1.1)
-: Not measured

The incidences of the main adverse events in foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201) are presented in Table 39. The incidence of fall tended to be higher in patients with non-V30M mutations, which is considered associated with many older and more severe patients enrolled into Study Fx1A-201 (5.3.5.2.2) as subjects with fall in this study tended to be older (62-76 years) and more severe at baseline (NIS-LL was 31.5-66.25). In Study Fx1A-201 (5.3.5.2.2), all subjects with dyspnoea had respiratory system disorder or cardiac disease potentially associated with dyspnoea and its causal relationship to tafamidis was denied for all cases.

Table 39. Incidences of main adverse events in foreign clinical studies

	Study Fx-005 (5.3.5.1.1)		Study Fx1A-201 (5.3.5.2.2)
	Placebo	Tafamidis	
N	63	65	21
Adverse events	96.8 (61)	92.3 (60)	81.0 (17)
Diarrhoea	17.5 (11)	26.2 (17)	23.8 (5)
Fall	1.6 (1)	0	23.8 (5)
Pain in extremity	9.5 (6)	16.9 (11)	19.0 (4)
Vomiting	12.7 (8)	10.8 (7)	14.3 (3)
Oedema peripheral	12.7 (8)	6.2 (4)	14.3 (3)
Dizziness	6.3 (4)	3.1 (2)	14.3 (3)
Dyspnoea	4.8 (3)	1.5 (1)	14.3 (3)
Nausea	12.7 (8)	12.3 (8)	9.5 (2)
Headache	19.0 (12)	15.4 (10)	4.8 (1)
Influenza	14.3 (9)	15.4 (10)	4.8 (1)
Nasopharyngitis	12.7 (8)	13.8 (9)	4.8 (1)
Back pain	6.3 (4)	7.7 (5)	4.8 (1)
Urinary retention	1.6 (1)	6.2 (4)	4.8 (1)
Urinary tract infection	12.7 (8)	23.1 (15)	0
Abdominal pain upper	3.2 (2)	12.3 (8)	0
Lacrimation decreased	11.1 (7)	9.2 (6)	0
Punctate keratitis	4.8 (3)	7.7 (5)	0
Myalgia	3.2 (2)	7.7 (5)	0
Pharyngitis	7.9 (5)	6.2 (4)	0
Erectile dysfunction	6.3 (4)	6.2 (4)	0
Thermal burn	7.9 (5)	6.2 (4)	0
Anxiety	4.8 (3)	6.2 (4)	0
Depression	4.8 (3)	6.2 (4)	0
Vaginal infection	1.6 (1)	6.2 (4)	0

Incidence (%) (n)

Based on the above, the efficacy and safety of tafamidis are unlikely to be substantially different between V30M and non-V30M patients and there is no need to limit the indication to patients with specific mutations.

4.(iii).B.(4).2) Patients with advanced disease

PMDA asked the applicant to describe why the indication for tafamidis in Europe has been limited to Stage 1 patients as defined by the clinical staging of TTR-FAP (Table 40, Glenner GG, et al., editors. *Amyloid and Amyloidosis*. Excerpta Medica; 1980:88-98, Ando Y, et al. *Orphanet J Rare Dis*. 2013;8:31) and then explain the appropriateness of not specifying the disease stage for use of tafamidis in Japan.

Table 40. Stages of TTR-FAP

	Stage 1	Stage 2	Stage 3
Ambulation status	No assistance required	Assistance required	Wheelchair bound or bedridden
Sensory involvement	Mild to moderate	Moderate to severe	Severe
Motor involvement	Mild	Mild to moderate	Severe
Limb involvement	Lower	Lower/limited upper	All
Autonomic involvement	Mild	Moderate	Severe
Disruption of daily activities	None to mild	Significant interference	Profound
Mean length per stage	4-5 years	3-4 years	2-3 years

The applicant explained as follows:
In Study Fx-005 (5.3.5.1.1), Karnofsky Performance Status Scale,[58)] instead of the clinical staging of TTR-FAP (Table 40), was used as a measure of physical function and patients with a Karnofsky Performance score of ≥50 were eligible. When subjects were assessed retrospectively for disease stage at the time of regulatory submission in Europe, 98% of the subjects (126 of 128 subjects) were of Stage 1 of the disease. Thus, in Europe, it was concluded that the efficacy of tafamidis in patients other than Stage 1 patients could not be assessed adequately. The NIS-LL and TQOL changes in three Stage 2 subjects enrolled into Study Fx-005 (5.3.5.1.1) or Study Fx1A-201 (5.3.5.2.2) were within the range of the changes observed in Stage 1 subjects.

Also in a Japanese phase III study (5.3.5.2.3, Study B3461010) as in Study Fx-005 (5.3.5.1.1), Karnofsky Performance Status Scale[58)] was used as a measure of physical function for patient enrollment and subjects were assessed retrospectively for disease stage. As a result, 30% of the patients (3 of 10 subjects) were of Stage 2 of the disease. In Study B3461010 (5.3.5.2.3), the NIS-LL changes from baseline to Week 52 in three Stage 2 subjects were -0.3, 1.7, and 10.6, respectively, and 2 of the 3 subjects were NIS-LL responders.[43)]

Regarding the safety of tafamidis in Stage 2 patients, adverse events reported by Stage 2 subjects enrolled into Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010) (Study B3461010 [5.3.5.2.3], 3 subjects; Study Fx-005 [5.3.5.1.1], 2 subjects; Study Fx1A-201 [5.3.5.2.2], 1 subject) were similar to those reported by Stage 1 subjects, and all events were mild or moderate in severity and a causal relationship to study drug was denied for all events except for “hiccups” in Study Fx-005 (5.3.5.1.1). It is unlikely that the safety of tafamidis differs substantially depending on disease stage.

Based on the above, the efficacy of tafamidis can be expected also in Stages 2 and 3 patients, inhibition of TTR tetramer dissociation by tafamidis does not differ substantially depending on the disease stage of patients, and there was no trend towards substantial differences in the safety of tafamidis in Stages 2 and 3 patients. On the other hand, TTR-FAP is a progressive, fatal, and rare disease and the only treatment expected to slow the progression of TTR-FAP symptoms, i.e. liver transplantation has limitations due to age requirement etc. and a lack of donors. Taking account of these points, the opportunity for Stages 2 and 3 patients to receive tafamidis should not be limited.

58)

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

4.(iii).B.(4).3) Post-liver transplant patients

As no data from a clinical study that evaluated the efficacy and safety of tafamidis in post-liver transplant patients have been submitted, PMDA asked the applicant to explain the efficacy and safety of tafamidis in these patients.

The applicant explained as follows:

Tafamidis has not been used in post-liver transplant patients in any of the Japanese and foreign clinical studies of tafamidis conducted and there are no data available regarding the efficacy and safety of tafamidis in this patient population. According to the post-marketing safety information for tafamidis (November 16, 2011 to November 15, 2012, the estimated total exposure, 165 patient-years), there was only 1 report of a patient with history of liver transplantation (deep thrombophlebitis of the leg) and the efficacy and safety of tafamidis in this patient population are undefined at present. Given that post-liver transplant patients are on immunosuppressant therapy and that tafamidis has been shown to increase the risk of urinary tract infection etc. [see "4.(iii).B.(3).1) Infections"], the safety of tafamidis is not considered comparable between post-liver transplant patients and patients with no history of liver transplantation. However, since (i) appropriate monitoring for infections is possible by closely observing the patient's symptoms, (ii) TTR-FAP is a progressive, fatal, and rare disease, and (iii) tafamidis has been shown to inhibit the dissociation of wild-type TTR as well [see "3.(i).A.(1) Primary pharmacodynamics"] and the efficacy of tafamidis is unlikely to be markedly different between post-liver transplant patients and patients with no history of liver transplantation, the opportunity for post-liver transplant patients to receive tafamidis should not be limited.

Based on the above, tafamidis should be indicated for patients with "transthyretin familial amyloid polyneuropathy", regardless of TTR mutation, disease stage, or history of liver transplantation. In Japanese and foreign clinical studies (5.3.5.1.1, Study Fx-005; 5.3.5.2.2, Study Fx1A-201; 5.3.5.2.3, Study B3461010), the efficacy of tafamidis in preserving the neurologic function of the lower limbs as measured by the NIS-LL (the primary efficacy endpoint) was suggested and furthermore, analyses of the secondary endpoints of Σ7 NTs NDS and Σ3 NTSF NDS also showed a trend towards preservation of neurologic function. Therefore, the appropriate indication statement should be "delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy".

PMDA considers as follows:

Concerning non-V30M patients, there are no data showing the rate of the progression of the disease due to each mutation and it is difficult to discuss the efficacy of tafamidis based on the similarity of the pathology of the disease between non-V30M and V30M patients. Also, baseline NIS-LL and TQOL scores were different between subjects enrolled into Study Fx-005 (5.3.5.1.1) and Study Fx1A-201 (5.3.5.2.2). Taking account of these points, it is difficult to conclude that these clinical study data have demonstrated the efficacy of tafamidis in non-V30M patients. In addition, there is limited clinical experience with tafamidis in Stages 2 and 3 patients and post-liver transplant patients, and thus it is difficult to discuss the efficacy and safety of tafamidis based on the currently available data. However, since (1) non-clinical pharmacology data indicate that inhibition of

TTR tetramer dissociation by tafamidis can be expected also in these patient populations; (2) due to limited numbers of these patients, it is difficult to conduct an additional clinical study to evaluate the efficacy and safety of tafamidis; and (3) the target disease of tafamidis, TTR-FAP, is a progressive, fatal, and rare disease for which the only available treatment alternative is liver transplantation and thus the medical need for tafamidis is high, the use of tafamidis in these patient populations may be acceptable, on condition that physicians in medical practice are fully informed that there are no or limited data in these patient populations and then advised to follow up patients carefully if tafamidis is used. Therefore, the proposed indication of "delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy" is acceptable, but the indication statement and precautions regarding the use of tafamidis in non-V30M patients, Stages 2 and 3 patients, and post-liver transplant patients will be finalized, taking account of comments from the Expert Discussion. It is necessary to continue to investigate the efficacy and safety of tafamidis in these patient populations via post-marketing surveillance and provide the information to medical practice appropriately if the important information on the risk/benefit of tafamidis becomes available.

4.(iii).B.(5) Dosage and administration for tafamidis

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration for tafamidis.

The applicant explained as follows:

Given that no clinical outcome measures exist for appropriate evaluation of the efficacy of tafamidis in TTR-FAP patients within a short period of time; and that as TTR-FAP is a rare disease, it is difficult to secure a sufficient number of patients, the applicant considered difficult to conduct a dose-finding study to determine the dose response etc. of tafamidis. A development plan was designed to determine the optimum dose of tafamidis based on pharmacology study data (Reference data, 4.2.1.1.5 and 4.2.1.1.7) and data on plasma tafamidis and TTR concentrations, the percent stabilization of TTR tetramer,[5)] etc. in a phase I study (5.3.3.1.2, Study Fx-002). Since the results from Study Fx-002 (5.3.3.1.2) etc. indicated that a plasma tafamidis:TTR stoichiometry of ≥1 would be necessary to inhibit TTR tetramer dissociation and the normal range of plasma TTR levels in healthy humans is between 18 and 38 mg/dL (3.2-6.8 μM),[59)] the lower limit of the effective plasma concentration range of tafamidis was estimated to be 3.2 to 6.8 μM. Furthermore, as the plasma tafamidis concentration at a dose of 15 mg ranged from 0.7 to 1.7 μg/mL (2.3-5.5 μM) in Study Fx-002 (5.3.3.1.2), the plasma tafamidis concentration at a dose of 20 mg was estimated to range from 1.5 to 2.2 μg/mL (4.9-7.1 μM). Consequently, a dose of 20 mg/day of tafamidis was selected for Study Fx-005 (5.3.5.1.1). Study Fx-005 (5.3.5.1.1) showed the efficacy of 20 mg/day of tafamidis and there were no major safety problems. Hence, a dosage of 20 mg/day of tafamidis was approved in Europe.

As a clinical pharmacology study in Japanese and non-Japanese healthy male volunteers living in the US (5.3.3.1.1, Study B3461009) showed no major differences in the pharmacokinetics of tafamidis and the percent

59) A reference range for plasma TTR concentrations was established at each laboratory and the above-mentioned reference range was established at Mayo Medical Laboratories. A recent report also states that TTR concentration in plasma normally ranges from 20 to 40 mg/dL (Sekijima Y, et al. *Familial Transthyretin Amyloidosis, GeneReviews*. 1993-2013).

stabilization of TTR tetramer[5] between Japanese and non-Japanese subjects, a dose of 20 mg/day of tafamidis was selected for a confirmatory study in Japanese TTR-FAP patients (5.3.3.2.3, Study B3461010) as for Study Fx-005 (5.3.5.1.1). Based on the results from Study B3461010 (5.3.3.2.3) and Study Fx-005 (5.3.5.1.1), the efficacy of tafamidis in Japanese TTR-FAP patients has been shown. Thus, a dosage of 20 mg/day of tafamidis should be recommended also in Japan.

PMDA considers that the above explanation is acceptable and that there is no particular problem with the proposed dosage and administration for tafamidis.

4.(iii).B.(6) Post-marketing commitments

PMDA considers as follows:

Since there is no definitive conclusion on the efficacy of tafamidis in delaying peripheral neurologic impairment and there are limitations on the efficacy evaluation based on the Japanese clinical study which included the limited number of patients, it is necessary to actively collect information on the long-term prognosis etc. of TTR-FAP patients treated with tafamidis via post-marketing surveillance in Japan, the international disease registry (THAOS),[53] etc. Physicians in medical practice should be appropriately informed that there is limited clinical experience with tafamidis in non-V30M patients, Stages 2 and 3 patients, and post-liver transplant patients. Furthermore, as the pharmacokinetics of tafamidis in patients with severe hepatic impairment have not been determined, it is necessary to provide an appropriate caution to medical practice, to obtain the plasma tafamidis concentration data as needed, and to promptly communicate the obtained findings to medical practice.

Since the limited number of patients were included in a Japanese clinical study and it is hard to say that sufficient safety information from foreign marketing experience has been accumulated, it is necessary to conduct a post-marketing drug use-results survey, which will cover all patients treated with tafamidis, and to continue to collect safety information in routine clinical settings. The occurrence of adverse events related to hepatotoxicity, hypersensitivity, reproductive and developmental toxicity, and immunotoxicity, safety in patients with severe hepatic impairment, efficacy in patients with non-V30M mutations, Stages 2 and 3 patients, and post-liver transplant patients, and the long-term efficacy of tafamidis (including long-term prognosis) need to be investigated via this survey. It is also necessary to collect the following information via post-marketing surveillance: the effects of the baseline demographics and disease characteristics of patients (gender, body weight, age, baseline NIS-LL and TQOL scores) on efficacy, efficacy and safety in patients with mild or moderate hepatic impairment, the occurrence of adverse events related to the inhibition of TTR function (adverse events related to thyroid function, vitamin A deficiency, increased blood glucose), skin adverse events, and gastrointestinal symptoms, and the risk of suicide-related adverse events.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2.3). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of tafamidis in delaying peripheral neurologic impairment in patients with TTR-FAP has been suggested and its safety is considered acceptable in view of its observed benefits. In Japan, there is no currently available effective pharmacotherapy for TTR-FAP. Tafamidis offers a new therapeutic option for peripheral neurologic impairment in patients with TTR-FAP and is considered to have clinical significance. The indication statement and the information regarding the use of tafamidis in non-V30M patients, Stages 2 and 3 patients, and post-liver transplant patients need to be further discussed at the Expert Discussion.

Tafamidis may be approved if it can be concluded based on the comments from the Expert Discussion that there are no particular problems.

Review Report (2)

August 2, 2013

I. Product Submitted for Registration

[Brand name]	Vyndaqel Capsules 20 mg
[Non-proprietary name]	Tafamidis Meglumine
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	February 13, 2013

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, 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).

Although the conclusions by PMDA stated in the Review Report (1) were supported by the expert advisors, PMDA conducted an additional review of the following points and took necessary actions.

(1) Efficacy of tafamidis

Although the efficacy of tafamidis is described in the "II.4.(iii).B.(2) Efficacy of tafamidis" section of the Review Report (1), the following points have been further clarified.

As a result of the evaluation of the clinical relevance of the treatment differences in the NIS-LL and TQOL changes, which were chosen as the co-primary endpoints for a foreign phase III study (5.3.5.1.1, Study Fx-005), PMDA considers that since no epidemiologic study on the NIS-LL and TQOL changes over time, the long-term prognosis, etc. in patients with transthyretin familial amyloid polyneuropathy (TTR-FAP) has been performed, it is difficult at present to clearly discuss how much the observed treatment differences for these endpoints contribute to an improvement in the long-term prognosis of TTR-FAP patients. However, PMDA has concluded that offering tafamidis to medical practice has significance at present, given that the results from the foreign phase III study (5.3.5.1.1, Study Fx-005) have suggested the efficacy of tafamidis and that TTR-FAP is an ultra-rare, fatal disease for which liver transplantation is the only treatment available, and based on the following points:

- As to the NIS-LL, one of the primary outcome measures, an expert consensus report states that a 2-point difference in NIS-LL scores between treatment groups is clinically meaningful (Dyck PJ, et al. *Ann Neurol*. 1995;38:478-482). In Study Fx-005 (5.3.5.1.1), the NIS-LL changes from baseline were 5.40 ± 8.66 in the placebo group and 2.19 ± 4.37 in the tafamidis group, and the treatment difference and its 95% confidence interval were -3.02 [-5.699, -0.348], showing a >2-point difference. As to the TQOL score, Σ7

NTs NDS,[46] Σ3 NTSF NDS,[47] and mBMI[48] as the efficacy endpoints, there is no consensus about the clinical relevance of the treatment difference, but the effect of tafamidis on various symptoms of TTR-FAP was assessed from different aspects, such as QOL, neurologic function, and general nutritional status. Consequently, the efficacy of tafamidis was suggested across all endpoints [see Table 25 and Table 26].

- The pathogenesis of TTR-FAP is due to deposition of insoluble fibrillar proteins (amyloid) derived from TTR in the nerves and tafamidis has been shown to inhibit TTR tetramer dissociation under various test conditions [see "II.3.(i).B.(1) Mechanism of action of tafamidis" of the Review Report (1)] and Study Fx-005 (5.3.5.1.1) suggested less deterioration in NIS-LL. Therefore, a consistent explanation can be given, to a certan extent, for the hypothesis for efficacy based on the pathogenesis of the disease and the pharmacological activity of tafamidis targeting the pathophysiology of the disease, and clinical study data on the clinical efficacy of tafamidis.

The FDA concluded that tafamidis [redacted] [see "II.4.(iii).B.(2).1).(c) Details of regulatory review in the US" of the Review Report (1)], whereas the EMA's Committee for Medicinal Products for Human Use (CHMP) considered that the risk-benefit balance of tafamidis is favorable, and its views on the efficacy of tafamidis were summarized as follows.

- NIS-LL and TQOL are scores mainly used for clinical evaluation of diabetic neuropathy. When the annual rate of change in the NIS-LL and TQOL scores was compared between an observational study Fx1A-OS-001 and the placebo group of Study Fx-005 (5.3.5.1.1), the results were similar between the two studies. Thus, these endpoints are clinically relevant in assessing disease progression in Stage 1 patients (a majority of the study population for these studies). The definition of NIS-LL responders (patients with a <2-point increase from baseline) and the study duration are acceptable.
- Differences between the treatment groups with respect to baseline NIS-LL and TQOL scores in Study Fx-005 (5.3.5.1.1) are no longer of concern because the adjusted analysis was statistically significant.
- In the primary analyses of Study Fx-005 (5.3.5.1.1), statistically significant differences between the placebo and tafamidis groups were not observed for either of the two co-primary endpoints. One of its reasons was study discontinuations due to liver transplantation. Taking also into account that patients were already on the liver transplant list before inclusion in the study and that study discontinuations due to liver transplantation were balanced between the treatment groups, pre-specified secondary analyses and additional analyses performed by changing the handling of patients who discontinued the study due to liver transplantation showed statistically significant difference in favor of tafamidis for the two co-primary endpoints. Therefore, the effects observed are clinically relevant.

(2) Indication for tafamidis

The following conclusion by PMDA was supported also at the Expert Discussion:

Tafamidis is indicated for "delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy" and the use of tafamidis in non-V30M patients, Stages 2 and 3 patients, and post-liver transplant patients is acceptable, on condition that the package insert contains relevant precaution statements (the efficacy and safety of tafamidis in these patients have not been established).

Based on the above, PMDA instructed the applicant to include the following statements regarding the use of tafamidis in non-V30M patients, Stages 2 and 3 patients, and post-liver transplant patients in the Precautions for Indications section of the package insert. The applicant accepted it.

[Precautions for Indications]

1. The efficacy and safety of the product in patients with advanced disease (patients who require assistance with ambulation, etc.) have not been established. [There is limited clinical experience in clinical studies.]
2. The efficacy and safety of the product in patients with transthyretin mutations other than V30M have not been established. [There is limited clinical experience in clinical studies.]
3. The efficacy and safety of the product in post-liver transplant patients have not been established [There is no clinical experience in clinical studies].

(3) Draft risk management plan

Taking account of the "II.4.(iii).B.(6) Post-marketing commitments" section of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA concluded that the applicant should include the safety specification and efficacy concerns as shown in Table 41 in the current draft risk management plan and should perform additional pharmacovigilance activities and risk minimization activities as shown in Table 42.

Table 41. Safety specification and efficacy concerns of draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
● None	● Hepatotoxicity ● Hypersensitivity reactions ● Reproductive and developmental toxicity	● Immunotoxicity ● Patients with severe hepatic impairment
Efficacy concerns		
● Efficacy in patients with mutations other than V30M ● Efficacy in Stages 2 and 3 patients ● Efficacy in post-liver transplant patients ● Long-term (≥1 year) efficacy		

Table 42. Summary of additional pharmacovigilance activities and risk minimization activities in draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
● Early post-marketing phase vigilance (EPPV) ● Specified drug use-results survey (all-case surveillance) ● Post-marketing clinical study[a)]	● Information provision by EPPV

a) After tafamidis is approved, Study B3461010 (5.3.5.2.3, ongoing) will be reclassified as a post-marketing clinical study and continued until tafamidis will become available at each medical institution.

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to address the above issues.

The applicant explained as follows:

A specified drug use-results survey, which will cover all patients treated with tafamidis, as shown in Table 43, will be conducted. In addition, treating physicians will be actively encouraged to participate in the THAOS[53)] as well as the specified drug use-results survey. Moreover, the results of the THAOS[53)] and the specified drug use-results survey will appropriately be communicated to healthcare professionals.

Table 43. Outline of specified drug use-results survey plan (draft)

Objective	Collect post-marketing information on the long-term safety (the occurrence of adverse drug reactions, etc.) and efficacy of tafamidis in patients treated with tafamidis in routine clinical settings.
Survey method	All-case surveillance
Patients to be surveyed	All patients treated with tafamidis
Observation period	3 years from the start of treatment with tafamidis
Main information to be collected	● Patient background (gender, body weight, age, TTR diagnosis,[a] severity,[b] history of organ transplantation, etc.) ● Dose, dosing frequency, duration of treatment ● Prior medications/prior therapy, concomitant medications/concomitant therapy ● Laboratory tests, ECG, echocardiography, pulse rate, blood pressure ● NIS, MRC (Medical Research Council Scale), QOL-DN, mBMI, ambulation status ● Occurrence of adverse events ● Priority item: hepatotoxicity

a) Results of genetic testing and tissue biopsy
b) Assessed using Karnofsky Performance Status Scale

PMDA accepted the above and concluded that the following condition for the approval of tafamidis should be imposed.

[Condition for approval]
Due to the very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey, which will cover all patients treated with the product, during the re-examination period, in order to obtain the background information of patients treated with the product, and at the same time to collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

(4) Update on ongoing Japanese phase III study

PMDA asked the applicant to provide an update on the occurrence of adverse events in the ongoing Japanese phase III study (5.3.5.2.3, Study B3461010).

The applicant explained as follows:
As adverse events collected between February 19, 2013 (the data cut-off date) and July 24, 2013, one death (completed suicide)[45] was reported, but its causal relationship to tafamidis was denied [see "II.4.(iii).B.(3).3) Central nervous system adverse events" of the Review Report (1) for details]. Other serious adverse events were reported by 2 subjects (decreased appetite and atrioventricular block second degree, 1 subject each), but a causal relationship to tafamidis was denied for both cases.

PMDA considers that there are no new concerns about the long-term safety of tafamidis, but it is necessary to further evaluate the long-term safety of tafamidis via post-marketing surveillance.

(5) Shelf-life of the product

Although a stability study (30°C/65% RH) was conducted with a view to recommending the storage conditions of store at "≤[redacted]°C" [redacted], the specification for [redacted] was not met at Month 24. In response to this result, taking also into account that room temperature is defined as between 1°C to 30°C, the applicant submitted an application to change the shelf-life of the product to 18 months when stored at room temperature.

PMDA accepted the shelf life of the product.

III. Overall Evaluation

As a result of its review, PMDA concludes that tafamidis may be approved for the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]

Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy

[Dosage and administration]

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

[Condition for approval]

Due to the very limited number of patients studied in Japan, the applicant is required to conduct a drug use-results survey, which will cover all patients treated with the product, during the re-examination period, in order to obtain the background information of patients treated with the product, and at the same time to collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.