CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211996Orig1s000 212161Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action:
Division of Cardiovascular and Renal Products; Office of Drug Evaluation-I

Date:	May 3, 2019
From:	Division of Cardiovascular and Renal Products (DCaRP): Martin Rose, MD, JD, Cross-Discipline Team Leader Norman Stockbridge, MD, PhD, Director Office of Drug Evaluation-I: Ellis F. Unger, MD, Director
Subject:	Summary Memorandum
NDAs:	NDA 211996 (priority) and NDA 212161 (standard)
Applicant:	FoldRx Pharmaceuticals (a subsidiary of Pfizer, Inc.)
Date of Submission:	11/02/2018 for both NDAs
PDUFA Goal Date:	7/2/2019 (priority) and 11/2/2019 (standard)
Proprietary Name:	Vyndaqel/Vyndamax
Established or Proper Name:	Tafamidis meglumine/Tafamidis (free acid)[1]
Proposed Dosage Forms:	Oral capsules 20 mg/Oral capsules 61 mg
Applicant Proposed Indications/Populations:	(b) (4)
Applicant Proposed Dosing Regimens:	80 mg (4 X 20 mg) once daily (meglumine salt) or 61 mg once daily (free acid) for each indication
Recommendation on Regulatory Action:	Approval of both NDAs with a common package insert
Final Indications/ Populations:	"Vyndaqel and Vyndamax are indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization."
Final Dosing Regimens:	As proposed by Applicant after discussions with FDA (see above)

[1] Depending on context, the term "tafamidis" may refer to tafamidis free acid or to either the free acid or meglumine salt. (b) (4) At their recommended daily doses (tafamidis meglumine 80 mg QD and tafamidis 61 mg QD), the drug products provide similar exposure to tafamidis in terms of AUC and can be considered therapeutically equivalent.

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1. Benefit-Risk

Benefit-Risk Integrated Assessment

Benefit-risk information for the CM indication is derived from ATTR-ACT, a global (predominantly US), randomized, double-blind, placebo-controlled trial in patients with mutant or wild-type ATTR-CM and New York Heart Association (NYHA) Class I-III symptoms. Patients were randomized in a 1:2:2 ratio to tafamidis 20 mg (n=88), 80 mg (n=176), or matching placebo (n=177) once daily in addition to standard of care. Randomization was stratified by the presence or absence of a variant TTR genotype and baseline NYHA Class. Patients were followed for 30 months after randomization. The primary endpoint was an assessment of time to all-cause death and the rate of CV hospitalizations, analyzed with the non-parametric Finkelstein-Schoenfeld (FS) test, which weighted deaths more heavily than hospitalizations.

Results for the prospectively planned primary endpoint and the analyses of each of its separate components strongly favored the pooled tafamidis arms over placebo. Based on the mean treatment effect in the study, treatment of 100 patients with tafamidis rather than placebo through 30 months would prevent 13 deaths – for a favorable number needed to treat (NNT) of 8. Importantly, the hazard ratio was not constant with respect to time, and so it is not possible to calculate the number of deaths prevented per year. The relative risk for cardiovascular hospitalizations was 0.68, i.e., a 32% relative reduction. Results for secondary endpoints, including changes from baseline in the 6-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, also strongly favored tafamidis over placebo. Thus, efficacy was shown with respect to four important but different parameters: improvement in survival, decreased hospitalization, better exercise performance, and less severe symptoms (a patient-reported outcome measure). Based on the results on exercise and symptoms, the drug does not appear to prevent or reverse disease progression, but over 30 months there was less progression in the pooled tafamidis groups than in the placebo group.

The trial did not identify any adverse drug reactions with tafamidis. Rates of AEs and discontinuations in the pooled tafamidis arms were similar to the rates in the placebo arm.

Thus, the trial results indicate that in patients with ATTR-CM, use of tafamidis confers substantial benefits in terms of survival and reductions in cardiovascular hospitalization, along with benefits in exercise tolerance and quality of life, without observed toxicity. The benefits of tafamidis strongly outweigh its risks. Because the benefits include improved survival along with reduced CV hospitalization in a multicenter trial with a persuasive *p*-value for the primary endpoint (0.0006), concordance of important secondary endpoints, and consistency among important subgroups, approval on the basis of a single study is entirely appropriate.

The two studied doses appeared similar in efficacy and safety. However, results for *ex vivo* TTR tetramer stabilization favor the 80 mg QD dose over the 20 mg QD dose, leading to the Applicant's choice of 80 mg QD as the recommended dose. In light of the lack of a toxicity signal, the review team agrees with the Applicant's choice of the 80-mg daily dose.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	ATTR-CM is a progressively debilitating condition. Rates of cardiovascular hospitalization and death are both high in patients with symptomatic ATTR-CM.	Overall, the median survival for patients with hereditary transthyretin amyloid cardiomyopathy (hATTR- CM) caused by the TTR Val122Ile mutation, the most common mutation associated with ATTR-CM and present in 3-4% of African Americans, is reported to be 2.5 years, whereas median survival for wild-type ATTR (wtATTR) is reported to be 3.6 years.
Current Treatment Options	There are no approved therapies for ATTR-CM.	Treatments for ATTR-CM are needed because of high rates of morbidity and mortality associated with this condition.
Benefit	The CM study met its primary endpoint of a reduction in the rate of mortality and/or CV hospitalization with a *p*-value of 0.0006 for the specified hierarchical, non-parametric FS test for the comparison of the pooled tafamidis meglumine arms vs. placebo. The FS test yields a test statistic, but not a hazard ratio (HR) or other easily interpretable summary of the results. However, using a Cox proportional hazards model, the HR for total mortality was 0.70 (95% CI, 0.51, 0.96). The relative risk ratio for the yearly rate of CV hospitalization was 0.68 (95% CI, 0.56, 0.81) using a Poisson regression analysis, again comparing the two active treatment arms vs. placebo. The two active treatment arms had similar efficacy results. See benefit-risk summary for additional information.	Results for the primary composite endpoint of death and CV hospitalizations provide substantial evidence of the effectiveness of tafamidis for treatment of ATTR-CM. Point estimates for the reductions in the rate of all cause death and CV hospitalizations with tafamidis compared to placebo were 30% and 32%, respectively. The NNT to prevent one death through 30 months is 8 (highly favorable).
Risk and Risk Management	AEs and discontinuations occurred at similar rates in the tafamidis and placebo groups; no adverse reactions were identified.	No special monitoring or REMS are required. Findings from animal studies suggested the possibility of fetal harm when tafamidis is administered to pregnant women; therefore, there will be a post-marketing requirement for a 10-year (or longer) pregnancy surveillance study in women exposed to tafamidis during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate.

2. Background

Pathogenesis of ATTR-CM [redacted] (b) (4) Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disease for which there are no therapies approved in the United States. In this condition, transthyretin homo-tetramers dissociate into monomeric components, become misfolded, and are deposited into tissues to which they are toxic. This disassociation of the tetramer into its monomeric components is thought to be the rate-limiting step in this cascade of events.

Monomeric misfolding may result from genetic mutations that alter the primary structure of the monomeric polypeptide, thereby destabilizing its properly folded secondary and tertiary structure. In these cases, mutations are hereditary, and ATTR-CM of this type is known as hATTR-CM. Also, genetically normal individuals with a normal TTR primary sequence (i.e., wild-type) can experience monomeric misfolding due to multiple epigenetic factors. This latter form of ATTR-CM typically affects the elderly and affects men more often than women. It is known as wild-type-ATTR or WT-ATTR-CM, or sometimes as age-related ATTR-CM.

The transthyretin tetramer has two thyroxine (T4) binding sites, for which it is a minor carrier. Tafamidis, which circulates as the free acid regardless of which drug product is administered, binds to one of the T4 binding sites, thereby stabilizing the tetramer and preventing its dissociation into monomeric components. The tetramer is also a carrier of the retinol/retinol-binding-protein complex. While the two T4 binding sites demonstrate negative cooperativity (the second T4 binding site will not bind T4 when the other is occupied), the biophysics of TTR binding to the retinol/retinol-binding-protein when tafamidis is bound to one of the T4 binding sites is unclear. This is relevant to maternal-fetal health because humans cannot synthesize retinol. The fetus is dependent on transplacental delivery of retinol which is important for fetal neural development, and TTR is potentially necessary for transplacental transfer of retinol.

Current Treatments for ATTR-CM: No specific drug treatments are approved for ATTR-CM in the US. FDA approved two drugs in 2018 for the treatment of ATTR polyneuropathy (ATTR-PN): patisiran and inotersen. Both drugs act by reducing the synthesis of TTR.

Diflunisal is an approved non-steroidal anti-inflammatory drug (NSAID) that is used off-label for ATTR, as it may improve TTR tetramer stability. Liver transplant is used to treat hATTR-CM because TTR amyloid is made in the liver.

Key events in the regulatory history of this and related submissions:

Tafamidis meglumine for hATTR-PN: NDA 202737

- May 2006: Orphan drug designation granted to Pfizer, Inc. for tafamidis for treatment of familial amyloid polyneuropathy
- June 2012: After a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, which favored denial of approval, the Office of Drug Evaluation-I issued a Complete Response Letter to the current Applicant for an ATTR-polyneuropathy (ATTR-PN) indication, [redacted] (b) (4)

Tafamidis meglumine and free acid for hATTR-CM (b) (4)

- February 2012: Orphan drug designation was granted Pfizer, Inc. for tafamidis meglumine for treatment of symptomatic ATTR-CM.
- (b) (4)
- May 2017: Fast Track granted
- May 2018: Breakthrough Therapy Designation granted
- 26 December 2018: NDA 211996 (tafamidis meglumine) accepted for filing and granted Priority review status. The sole indication sought was TTR-CM (b) (4)
- 10 January 2019: NDA 212161 (tafamidis free acid) accepted for filing and granted Standard review status. The sole indication sought was TTR-CM. (b) (4)

3. Product Quality

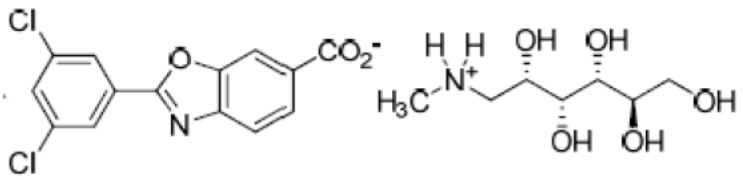
The product quality team recommends approval of both of the tafamidis NDAs. The two drug products will be discussed separately.

3.1 NDA 211996 – Tafamidis meglumine 20 mg oral capsules

The product quality team included:

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Charles Jewell		Office of New Drug Products (ONDP)
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee	
Labeling			
Environmental	James Laurenson		
Manufacturing	Frank Wackes	Ying Zhang	Office of Process and Facilities (OPF)
Biopharmaceutics	Kaushalkumar Dave	Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams		Office of Program and Regulatory Operations (OPRO)
Application Technical Lead	Wendy Wilson-Lee		ONDP

Figure 1: Structure of Tafamidis Meglumine



The molecular formula of tafamidis meglumine is $C_{14}H_7Cl_2NO_3 \cdot C_7H_{17}NO_5$, and its molecular weight is 503.33 Daltons.

Drug Substance: The drug substance is synthesized from tafamidis free acid. It is crystalline and has one polymorph. [redacted] (b) (4) Hygroscopicity and polymorph interconversion were assessed and were not an issue for this application. Tafamidis free acid, the circulating form and active moiety, has no chiral centers.

The review states,

> "Because of the low solubility of the drug substance, the particle size is critical attribute. The particle size for the clinical batches ranged as follow: [redacted] (b) (4) is reasonable."

There are no other issues.

Drug Product: The drug product is a soft gelatin capsule containing 20 mg of the drug substance [redacted] (b) (4) There are no issues.

Stability: The primary CCS is foil/foil blisters, 10 capsules per blister. The secondary CCS is a carton of 4 intermediary cartons. Each intermediary carton contains 3 blister cards, for a total of 120 capsules per secondary CCS. Stability data provided in the NDA support the requested shelf life of 24 months.

The Applicant commits to continue the stability evaluation of the registration batches through 36 months (5°C/ambient RH, 25°C/60%RH, 30°C/75%RH). At least one annual batch will be placed on stability through 24 months (25°C/60%RH only). OPQ found this to be adequate.

Biopharmaceutics: The Biopharmaceutics reviewers recommend approval. Their review focused on: 1) the proposed dissolution method and acceptance criteria; and 2) formulation bridging.

The dissolution method was deemed acceptable for quality control of the proposed finished drug product. The proposed acceptance criterion, not less than (b) (4)% in 30 minutes, is likewise acceptable.

The reviewers concluded that *in vitro* bridging studies are not needed for the proposed product because the Applicant performed a comparative bioavailability study (Study # B3461044) comparing the pre-change (manufactured at (b) (4) and the post-change/to-be-marketed products (manufactured at Catalent). They note the results of this study will be evaluated by OCP (see Section 5).

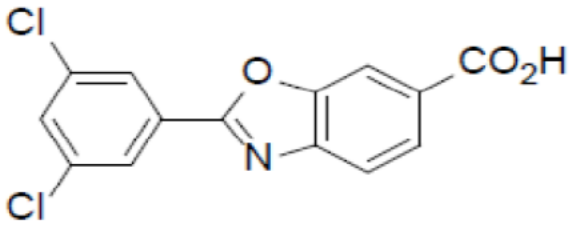
Facilities: Four facilities are described that are involved in manufacturing, testing and/or packaging the drug substance or drug product. Three of these are contract facilities in the US, and one is a Pfizer facility in Ireland that is the only site now planned for drug substance manufacturing and testing. All are recommended for approval. There are no recommended PMCs, planned post-approval inspections, or lifecycle management considerations.

3.2 NDA 212161 – Tafamidis 61 mg oral capsules

The CMC team for this NDA had the same members as the one for the tafamidis meglumine NDA previously discussed in this section. They recommend approval.

Drug Substance: The drug substance in this capsule is the free acid of tafamidis. It is the active moiety in tafamidis meglumine, the drug substance used in the CM (b) (4)

Figure 2: Structure of Tafamidis



(b) (4)

The molecular formula of tafamidis is $C_{14}H_7Cl_2NO_3$ and its molecular weight is 308.12 Daltons.

Tafamidis has 3 polymorphs. The one used as the drug substance is thermodynamically stable. Like the meglumine salt, the free acid is poorly soluble in water.

Drug Product: Like the tafamidis meglumine product, the free acid drug product is a gelatin capsule containing a suspension of the drug substance, tafamidis (61 mg), (b) (4)

Stability: The primary commercial CCS is a (b) (4) foil/foil blister pack with peel/push lidding (10 capsules per blister). The secondary CCS is a carton containing 3 blister cards, for a total of 30 capsules per carton. The data in the NDA support the requested expiration dating of 24 months.

The Applicant has committed to evaluate the stability of the primary stability batches through 36 months. At least one annual batch will be placed under long-term stability evaluation.

Biopharmaceutics: The reviewers recommend approval of the free acid product. Their comments are similar to those described for the meglumine salt product. The review states that the approval of tafamidis free acid is supported by the findings of the study comparing the pharmacokinetics (PK) of the free acid product (61 mg) and the meglumine salt product (4 X 20 mg), although the OCP review of this study is not cited. For more information about this bioequivalence study, see Section **5**.

Facilities: The four facilities for the manufacturing, testing, and packaging the tafamidis free acid drug substance product are the same as for the meglumine salt. They are all acceptable.

There are no recommended PMCs, post-approval inspections, or lifecycle management considerations.

4. Nonclinical Pharmacology/Toxicology

The DCRP nonclinical pharmacology review was performed by Drs. William Link and Jean Wu. They recommend approval. Parts of their review are based on the prior nonclinical review of tafamidis meglumine in NDA 202737 by Drs. David Hawver in the Division of Neurology Products (DNP), who also recommended approval.

General toxicology studies in rats treated for up to 26 weeks yielded a no adverse observable effect level (NOAEL) of 30 mg/kg/day, which was the highest dose tested. The human equivalent dose (HED) based on standard inter-species ratios for mg/kg dosing is 4.8 mg/kg/day. In humans, AUC_{0-24h} at the recommended dose of 80 mg tafamidis meglumine daily was 166.2 μg·hr/mL, with a Cmax of 9.1 μg/mL

In the 39-week oral toxicity study in dog, the NOAEL was again the highest dose tested, 45 mg/kg/day. The HED to this dose in dogs based on mg/kg conversion is 25 mg/kg/day. In the dogs, the Day 271 AUC_{0-24hr} was 8.5 μg·hr/mL in males and 10.6 μg·hr/mL in females.

Tafamidis free acid was negative for genotoxicity in an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay in human lymphocytes, and an *in vivo* rat micronucleus assay. Carcinogenicity testing in mice and rats was negative.

In male and female rats, mating, fertility and early embryonic development were not affected by dosing with tafamidis meglumine at doses of 5, 15, or 30 mg/kg/day. Males were dosed for 28 days prior to and then during the 21-day mating period to the day before euthanasia. Females were dosed for 15 days before mating, throughout mating, and to gestation day (GD) 7.

There were adverse findings in animals dosed at later stages of pregnancy, some of which will be included in labeling:

- In a rat embryo-fetal development (EFD) study, pregnant rats received vehicle or tafamidis meglumine at 15, 30, or 45 mg/kg/day once daily by gavage from gestational day (GD) 7 through GD 17. Maternal toxicity including death was observed at 45 mg/kg/day, and fetal body weights were decreased at ≥30 mg/kg/day. There were no test article-related external, visceral, or skeletal variations or malformations at any dose. The NOAEL for maternal toxicity was 30 mg/kg/day, with an associated GD 17 AUC_{24} of 1610 μg•h/mL. The NOAEL

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for developmental toxicity was 15 mg/kg/day, which was associated with GD 17 AUC_{24} of 1090 μg•h/mL. Tafamidis meglumine was not teratogenic in rats.

- In a rabbit EFD study, pregnant rabbits were administered vehicle or tafamidis meglumine at 0.5, 2, or 8 mg/kg/day once daily by oral gavage from GD 7 to GD 19. Mortality, body weight loss, and lower food consumption were observed at 8 mg/kg/day. Increased post-implantation loss, decreased fetal body weights, and several types of eye malformations in three fetuses from 2 litters were observed at 8 mg/kg/day. Increased incidence of alterations in the nasal bones (≥0.5 mg/kg/day) and supernumerary thoracic ribs and thoracic vertebrae (≥2 mg/kg/day) were observed. The NOAEL for development could not be identified.
- In the pre/postnatal development study, rats were administered vehicle or tafamidis meglumine at 5, 15, or 30 mg/kg/day once daily by oral gavage from GD 7 to lactation day (LD) 20. Because of high mortality (no surviving pups in 20 of 25 litters by LD4), dosing at 30 mg/kg/day was terminated early in the lactation period and surviving rats and pups were euthanized. At 15 mg/kg/day, 4 of 25 females were euthanized on LD 2 or LD 3 because they had no surviving pups. Reduced survival, birth weight, postweaning body weight, delayed male sexual maturity, and impaired learning and memory were observed in the offspring of dams dosed at 15 mg/kg/day. The NOAEL for pre/postnatal development was 5 mg/kg/day.
- Pregnant and lactating female rats were administered repeated daily oral doses of tafamidis meglumine (15 mg/kg/day) followed by a single oral gavage dose of [14C]-tafamidis meglumine on Day 4 or 12 postpartum. Radioactivity in milk was observed by 1 hr post-dose on Day 4 and Day 12, increasing thereafter to peak levels at 8 and 24 hrs post-dose, respectively. The ratio of the highest radioactivity associated with [14C]-tafamidis meglumine in milk (8 hours post-dose) vs. plasma (1 hour post-dose) was approximately 1.6 on Day 12, indicating tafamidis meglumine is present in milk after oral administration.

These findings are reflected in the agreed-upon labeling.

5. Clinical Pharmacology

The OCP reviewers were Drs. Snehal Samant, Ruojing Li, Chao Liu, Sudharshan Hariharan, and Mehul Mehta. They recommend approval of both tafamidis meglumine and tafamidis free acid for use in patients with ATTR-CM.

Pharmacokinetics: Most of the PK information in the review is based on studies of tafamidis meglumine. Information regarding the PK of tafamidis free acid (tafamidis) comes from a bioequivalence study comparing tafamidis to tafamidis meglumine.

T_{max} of tafamidis meglumine occurred within 4 hours after ingestion of tafamidis meglumine. Exposure is dose proportional for single dosing up to 480 mg and multiple dosing up to 80 mg once daily. Administration of a high-fat, high-calorie meal did not cause a clinically significant difference in pharmacokinetics.

The volume of distribution of tafamidis is about 16 L. Protein binding is >99% *in vitro*. Binding is primarily to TTR tetramers.

The effective half-life of tafamidis is ~33 hours and the terminal elimination half-life is ~49 hours. Accumulation ratios with once daily dosing ranged from 2.1 to 2.7. The apparent oral clearance of tafamidis is 0.228 L/h. The metabolism of tafamidis has not been fully characterized. After a single oral dose of tafamidis meglumine 20 mg, approximately 59% of the dose was recovered in feces,

mostly as unchanged drug. About 22% of the dose was recovered in urine (mostly as the glucuronide metabolite). Phase II enzymes uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9, UGT1A1, and UGT1A3 appear to be the major isoforms responsible for the formation of the acyl glucuronide, while minor activity was observed with UGT isoforms 1A6, 1A7, 1A8, and 2B7.

Tafamidis PK was not affected by age over the range of 18-88 years, race (Caucasian vs. Japanese) or renal impairment. Intra-subject variability for tafamidis C_{max} and $AUC_{0\text{-last}}$ ranges from 11% to 24%. Tafamidis PK is similar between healthy adults and ATTR-CM patients.

Patients with moderate hepatic impairment (Child-Pugh Score of 7 to 9) had decreased systemic exposure (approximately 40%) and increased clearance (approximately 67%) of tafamidis compared to healthy subjects. But because TTR tetramer levels are lower in subjects with moderate hepatic impairment than in healthy subjects, the tafamidis exposure relative to the amount of TTR tetramer is high enough to maintain the level of TTR tetramer stabilization in these patients compared to healthy subjects. No clinically significant difference in the pharmacokinetics of tafamidis was observed in patients with mild hepatic impairment (Child Pugh Score of 5 to 6) compared to healthy subjects. The effect of severe hepatic impairment on tafamidis is not known.

The OCP review summarizes information on drug-drug interactions as follows:

> "Clinical Studies
> No clinically significant difference in the pharmacokinetics of midazolam (a CYP3A4 substrate) or on the formation of its active metabolite (1 hydroxymidazolam) was observed when a single 7.5 mg dose of midazolam was administered prior to and after a 14-day regimen of tafamidis meglumine 20 mg once daily.
>
> In Vitro Studies
> Cytochrome P450 Enzymes: Tafamidis induces CYP2B6 and CYP3A4 and does not induce CYP1A2. However, static-mechanistic model predictions show that the potential of tafamidis meglumine 80 mg once daily to induce CYP3A4 or CYP2B6 is low. Tafamidis does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 or CYP2D6.
>
> UGT: Tafamidis inhibits UGT1A1. However, it does not induce or inhibit other UGT substrates.
>
> Transporter Systems: Tafamidis inhibits BCRP and organic anion transporters OAT1 and OAT3. Tafamidis did not show a potential to inhibit P-glycoprotein (P-gp), organic cation transporter OCT2, organic anion transporting polypeptide OATP1B1 and, OATP1B3, and multidrug and toxin extrusion transporters MATE1, and MATE2K at clinically relevant concentrations."

In addition, OCP recommended the following language for Sec. 7:

> "7.1 BCRP substrates
> Tafamidis inhibits breast cancer resistant protein (BCRP) in vitro and may increase exposure of substrates of this transporter (e.g., methotrexate, rosuvastatin, imatinib) following 80 mg tafamidis meglumine. Dose adjustment may be needed for these substrates."

Pharmacodynamics: The Applicant characterized the relationship between the molar ratio of tafamidis:TTR tetramer and TTR tetramer stabilization based on a population PK-PD analysis of data from 11 studies. The relationship was adequately described by a sigmoid E_{max} model. Healthy volunteers demonstrated the greatest TTR tetramer stabilization, followed by patients with ATTR-PN, and then patients with ATTR-CM. Percent stabilization increased with increasing tafamidis:TTR

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molar ratio, which increased with tafamidis dose. The Applicant was not able to establish a relationship between dose, exposure, or percent stabilization and clinical benefit (the primary endpoint of death or cardiovascular hospitalization). Fortunately, the success of the tafamidis applications does not require the establishment of that relationship.

Bioequivalence Studies:

Study B3461044

The 20 mg tafamidis meglumine capsules initially used in the confirmatory ATTR-CM study were manufactured by [redacted] (b) (4) The source was changed to Catalent Pharma Solutions (Catalent) during the study, and Catalent will manufacture the to-be-marketed capsules. Study B3461044 was an open-label, randomized, two-treatment, two-sequence, single-dose cross-over trial in 26 healthy volunteers, to compare tafamidis meglumine from the two sources. The washout period between doses was ≥ 20 days. The [redacted] (b) (4) product was considered the reference material. Study results are shown in Table 1. The results establish the bioequivalence of the two formulations. Concentration-time profiles for the two products were essentially superimposable. By visual inspection of concentration-time profiles, the mean effective half-life of both products was approximately 36 hours, with a mean terminal half-life of 48 to 50 hours.

Table 1: Study B3461044 – Plasma PK Parameters

Parameter (units)	Tafamidis 20 mg Capsule - Catalent	Tafamidis 20 mg Capsule - [redacted] (b) (4)
N, n	25, 24	26, 24
AUCinf (μg•h/mL)	63.3 (0.02)	63.2 (0.02)
AUClast (μg•h/mL)	59.2 (0.02)	58.8 (0.02)
Cmax (μg/mL)	1.2 (0.02)	1.2 (0.02)
Tmax (h)	2.00 (0.50-6.05)	2.00 (0.50-8.00)
Mean residence time (h)	67.5 ± 15.4	69.6 ± 16.0
Terminal t½ (h)	48.1 ± 10.9	49.8 ± 11.6

Source: adapted from Table 10, Study B3461044 CSR. %CV = percentage coefficient of variance; N = Number of subjects in the treatment group; n = Number of subjects where AUC_{inf}, t½, and MRT were determined [redacted] (b) (4) SD = standard deviation. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (±SD) for MRT and t½.

Study B3461054

Study B3461054 compared the PK of tafamidis meglumine (four 20 mg capsules) to a single tafamidis free acid 61 mg capsule. This was an open-label, randomized, 4-period, 4-sequence trial in volunteers that including a food effects component. Results are shown in Table 2 and establish that there is a food effect on C_{max}, but not AUC, for both products. Notably, for the meglumine salt, fasted subjects had higher C_{max} than fed subjects; the opposite was observed for the free acid. In addition, the free acid formulation provides higher exposure in terms of AUC than the meglumine salt regardless of food. However, differences between the two products in C_{max} and AUC were modest – no more than 20% to 24%.

Table 2: Study B3461054 – Comparative PK and Food Effects for Tafamidis 61 mg vs. Tafamidis Meglumine 4 x 20 mg

	PK Parameter (units)	Geometric Least Square Mean (%CV)		Ratio Test/Reference (%) (90% C.I.)
		Test	Reference	
Tafamidis 61 mg free acid Capsule (Test) vs. Tafamidis meglumine 4 × 20 mg Capsules (Reference)				
Relative BA Fasted state	$AUC_{0\text{-}inf}$ (ng.h/mL)	233700 (12)	203400 (18)	114.9 (106.7, 123.7)
	C_{max} (ng/mL)	3857 (19)	4835 (20)	79.8 (72.8, 87.4)
Relative BA Fed state	$AUC_{0\text{-}inf}$ (ng.h/mL)	247900 (20)	208100 (23)	119.2 (110.5, 128.5)
	C_{max} (ng/mL)	5106 (16)	4132 (15)	123.6 (112.9, 135.2)
Fed state (Test) vs. fasted state (Reference)				
Food effect Tafamidis free acid	$AUC_{0\text{-}inf}$ (ng.h/mL)	247900 (20)	233700 (12)	106.1 (98.4, 114.4)
	C_{max} (ng/mL)	5106 (16)	3857 (19)	132.4 (121.0, 144.9)
Food effect Tafamidis meglumine	$AUC_{0\text{-}inf}$ (ng.h/mL)	208100 (23)	203400 (18)	102.30 (95.0, 110.1)
	C_{max} (ng/mL)	4132 (15)	4835 (20)	85.5 (78.0, 93.6)

Source: OCP Reviewer's analysis

Study B3461056

This was an open-label, randomized, 2-period, 2-sequence, crossover, multiple-dose bioequivalence study in fasted healthy volunteers comparing PK at steady state of 61 mg tafamidis free acid soft gelatin capsules (test) and 4 × 20 mg commercial tafamidis meglumine soft gelatin capsules (reference). Study medication was given daily for 7 days with PK parameters assessed on Day 7. Results are displayed in Table 3. OCP concluded that the two tested products are bioequivalent.

Table 3: Summary of Plasma Tafamidis Pharmacokinetic Parameter Values on Day 7 Following Multiple Oral Doses

Parameter (Units)	Tafamidis Free Acid 61 mg Capsules	Tafamidis Meglumine 4 × 20 mg Capsules	Test/Reference Ratio (95% CI)
N, n	30, 30	30, 30	
AUC_{tau} (μg•hr/mL)	170.0 (0.02)	166.2 (0.020)	102.3 (98.0, 106.8)
C_{max} (μg/mL)	8.6 (0.02)	9.1 (0.02)	94.1 (89.1, 99.4)
T_{max} (hr)	4.0 (2.0-8.0)	2.0 (0.50-6.0)	-
C_{min} (μg/mL)	5.4 (0.03)	4.9 (0.03)	-

Notes: Tafamidis free acid 61 mg is "test" and tafamidis meglumine 4 x 20 mg is "reference." PK parameters except T_{max} are geometric least square means (%CV). T_{max} is expressed as median (range). Time "Tau" is 24 hours after the Day 7 (last) dose. Source: Adapted from OCP reviewer's analysis.

6. Clinical Microbiology

The microbiological quality of both proposed products is acceptable. Both products are non-sterile oral capsules and have been tested in line with USP <1111> recommendations for microbiological

quality of non-sterile, (b) (4) preparations for oral use. Testing was done on the clinical batches and the registration batches manufactured at the commercial site.

Microbiological acceptance criteria for both drug products have been omitted from the specifications by the Applicant. OPQ has agreed.

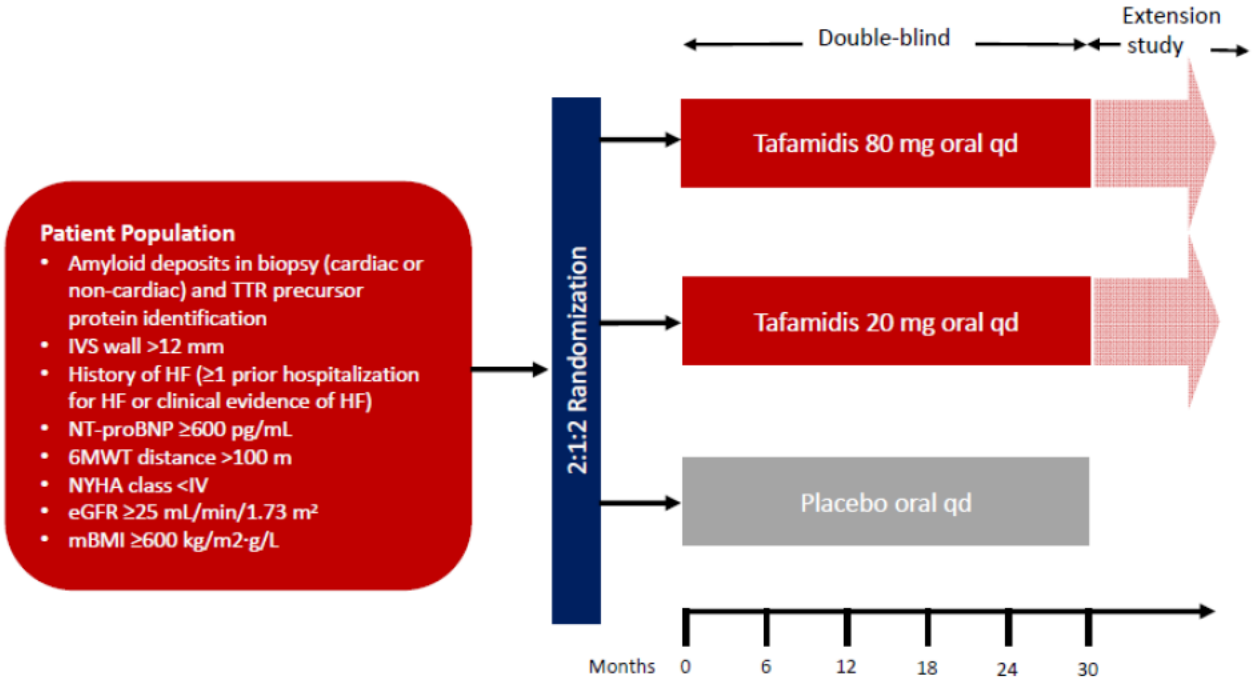
7. Clinical/Statistical- Efficacy

The clinical reviewers were Drs. Preston Dunnmon (efficacy) and Tzu-Yun McDowell (safety). The statistical reviewers were Drs. Jialu Zhang and James Hung. This review borrows heavily from their excellent reviews.

Study B3461028:

All clinical evidence establishing the efficacy of tafamidis for its proposed ATTR-CM indication and most of the safety information for that indication come from Study B3461028, known as ATTR-ACT, an international, double-blind, RCT comparing two doses of tafamidis meglumine, 20 mg QD and 80 mg QD (given as 4 x 20 mg capsules) vs. matching placebo. Results of the study have been published (Maurer MS, et al. *N Engl J Med* 2018; 379:1007). The schematic design of the study is shown in Figure 3. Randomization was 2:1:2 to the 80 mg, 20 mg, and placebo arms, respectively.

Figure 3. ATTR-ACT Plan



Diagnostic criteria:

- Diagnosis of either hATTR-CM or wtATTR-CM, defined by genotype. For variant-genotype-positive subjects with a monoclonal gammopathy of undetermined significance (MGUS) based on serum or urine light chain determinations, the diagnosis of ATTR amyloidosis was to be confirmed as described in the criteria below for wtATTR-CM.

  Variant-genotype-negative subjects were required to demonstrate the presence of amyloid deposits in a biopsy tissue, with TTR precursor protein identification by immunohistochemistry, scintigraphy or

mass spectrometry. When immunohistochemistry (IHC) was equivocal, diagnosis had to be confirmed using one of the following: a) mass spectrometry; b) immunohistochemistry with electron microscopy, immunoelectron microscopy, or immune-gold microscopy; c) scintigraphy with tracer, e.g. ^{99m}TC-DPD (3,3-diphosphono-1,2-propano-dicarboxylic acid), ^{99m}TC- PYP (pyrophosphate) or ^{99m}TC-HMDP (hydroxymethylene diphosphonate).
- End-diastolic interventricular septal thickness >12 mm by echocardiography

Inclusion criteria:
- Age 18 to 90 years
- Hospitalized for heart failure (HF) or required diuretic therapy at least once, but clinically stable with no cardiovascular hospitalizations within 2 weeks prior to baseline
- NT-proBNP concentration >600 pg/mL (note: no separate criterion for those with atrial fibrillation)
- Ability to complete > 100 meters on the 6-Minute Walk Test (6MWT)

Exclusion criteria:
- Uninterpretable echocardiograms for wall thickness at screening
- Use of non-allowed medications within 30 days prior to baseline (e.g. diflunisal, taurourso-deoxycholate and doxycycline)
- Modified body mass index (mBMI) < 600 kg/m^2•g/L (note: mBMI includes serum albumin concentration in g/L as a term)
- Previous use of tafamidis
- Ongoing treatment with calcium channel blockers or digitalis
- Primary (light chain) amyloidosis
- Prior recipient of heart and/or liver transplants or an implanted cardiac mechanical assist device
- Renal failure requiring dialysis and/or an estimated glomerular filtration rate (eGFR) of less than 25 mL/min/1.73 m^2
- Self-catheterization required for urinary retention
- New York Heart Association (NYHA) Functional Class IV
- History of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker was indicated but had not be placed
- Heart failure on the basis of ischemic heart disease (e.g., prior myocardial infarction) or uncorrected valvular disease not primarily due to ATTR-CM

The primary endpoint was a comparison of all-cause mortality and the rate of cardiovascular hospitalization in the pooled tafamidis arms vs. placebo. The specified analysis was a hierarchical, non-parametric procedure based on a Wilcoxon rank sum test, described by Finkelstein and Schoenfeld in 1999.[2]

The statistical review describes this analysis as follows:

"The proposed primary analysis, Finkelstein-Schoenfeld (FS) analysis, is a score test based on the sum of scores for the treatment group. The method combined all-cause mortality and CV hospitalization frequency. The test score was computed using a pairwise ranking procedure. The test statistic was based on the sum of these scores and was stratified by TTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III).

Within each stratum, each subject was compared to every other subject in a pair-wise manner. The pair-wise comparison assigned a +1 to the "better" subject and a -1 to the "worse" subject. All-cause mortality was given higher priority in the calculation and only when two given subjects tied on all-cause mortality then CV

[2] Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999; 18:1341-1354.

Reference ID: 4428559

hospitalization frequency would be used in the comparison. Comparisons of cardiovascular related hospitalization frequency for subjects who completed all 30 months study duration were based on the earlier of the two actual study durations. Subjects, who discontinued for transplantation or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death.

- If both subjects were dead, then the subject with a longer survival time was assigned +1.
- If one subject was alive and the other was not, the live subject received a +1 and the deceased one a -1.
- If both subjects were alive, the comparison used cardiovascular-related hospitalization to assign scores. The subject with the fewer cardiovascular related hospitalization (frequency) received a +1 while the other received -1.
- In the case where one subject was censored before a second subject died, and where the vital status of the first subject at Month 30 was missing, the frequency of cardiovascular- related hospitalizations at the shorter of their follow-up times was used to assign +1 or -1.

The proposed test is a score test based on the sum of the scores for the treated group."

Success for this analysis would support the logical inference that the pooled tafamidis arms were superior to placebo for effects on either all-cause death, the rate of cardiovascular hospitalizations, or both. One would need to perform additional analyses to understand the effects of either of the individual doses used in the study and the effects of tafamidis on the individual components of the composite primary endpoint.

Only two of the many secondary endpoints in the Statistical Analysis Plan (SAP) were allocated alpha in the hierarchical alpha-sparing plan. These were the "key secondary analyses." If the analysis of the primary endpoint was successful, the available alpha (0.05) would be passed sequentially to:

1) Change from Baseline to Month 30 in the distance walked during 6-Minute Walk Test (6MWT). If that analysis was successful, the alpha would be passed to
2) Change from Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).

The protocol indicates that the target sample size of about 400 subjects was based on the following assumptions:

> "…an all-cause mortality rate of 12.5% for the tafamidis group and 25% for the placebo group and 1.5 cardiovascular-related hospitalizations for the tafamidis group and 2.5 cardiovascular-related hospitalizations for the placebo group. With a treatment duration of 30 months and a significance level (alpha) of 0.05 (two-sided test), a sample size of 300 (n=120 for placebo, n=60 for 20 mg, and n=120 for 80 mg) yields a power over 90% (for the primary comparison), which assumes pooling of the tafamidis 20 mg and 80 mg dose groups. An alternative assumption of 30% reduction in mortality (17.5 % for tafamidis and 25% for placebo) yields a power of approximately 80%. Sample size estimation was performed based on simulations, given that no closed-form sample size estimation solution is available for the primary analysis method."

Results:

Baseline patient characteristics are shown in Table **4**. Most patients (61-72%) were enrolled at US sites. As expected, most subjects were male and had wild-type ATTR-CM. The percentage of patients with Class III HF (the worst class allowed into the study) was slightly higher in the placebo arm than in the pooled tafamidis arms (36% vs. 30%). However, the analysis of the primary

endpoint was stratified by this factor, thus minimizing the potential effect of this modest imbalance on study outcomes.

Table 4: Patient Demographic and Baseline Characteristics in ATTR-ACT (ITT Population)

		Tafamidis 20 mg	Tafamidis 80 mg	Pooled Tafamidis	Placebo
N		88	176	264	177
Age	Mean (SD)	73.3 (7.1)	75.2 (7.2)	74.5 (7.2)	74.1 (6.7)
Gender	Male (%)	83 (94)	158 (90)	241 (91)	157 (89)
	Female (%)	5 (6)	18 (10)	23 (9)	20 (11)
Race	White (%)	75 (85)	136 (77)	211 (80)	146 (83)
	Black (%)	11 (13)	26 (15)	37 (14)	26 (15)
	Asian (%)	2 (2)	11 (6)	13 (5)	5 (3)
	Other (%)	0	3 (2)	3 (1)	0
Country	US (%)	63 (72)	108 (61)	171 (65)	108 (61)
	Non-US (%)	25 (28)	68 (39)	93 (35)	69 (39)
Baseline NYHA class	Class I or II (%)	65 (74)	121 (69)	186 (70)	114 (64)
	Class III (%)	23 (26)	55 (31)	78 (30)	63 (36)
TTR Genotype	Wild (%)	67 (76)	134 (76)	201 (76)	134 (76)
	Variant (%)	21 (24)	42 (24)	63 (24)	43 (24)

Source: Statistical Reviewer's Table

Patient disposition in ATTR-ACT is shown in Table 5. Loss to follow-up was uncommon in the study as a whole. Withdrawals were more common in the placebo arm than in either tafamidis arm.

Table 5: Patient Disposition in ATTR-ACT (ITT Population)

		Tafamidis 20 mg	Tafamidis 80 mg	Pooled Tafamidis	Placebo
N		88	176	264	177
Completed (%)	Total (%)	60 (68)	113 (64)	173 (66)	85 (48)
Discontinued	Total (%)	28 (32)	63 (36)	91 (34)	92 (52)
	Death (%)	14 (16)	25 (14)	39 (15)	38 (22)
	AE (%)	5 (6)	12 (7)	17 (6)	11 (6)
	Subject no longer willing to participate (%)	8 (9)	17 (10)	25 (9)	37 (21)
	Protocol violation	0	1 (1)	1 (0.4%)	1 (1)
	Loss to follow-up	0	1 (1)	1 (0.4%)	0
	Cardiac device implantation	0	2 (1)	2 (1)	0
	Organ transplantation	1 (1)	3 (2)	4 (2)	4 (2)
	Other	0	2 (1)	2 (1)	1 (1)

Source: Adapted from Statistical Reviewer's Table

Primary Endpoint Results:

The primary endpoint results are shown in Table 6 and Table 7. The study easily met its primary endpoint. Arm-specific data in Table 7 indicate that the tafamidis meglumine 20 mg and 80 mg were similar in their effects on both all-cause mortality and cardiovascular hospitalization.

Table 6: Finkelstein-Schoenfeld Analysis of Primary Endpoint and Sensitivity Analyses in ATTR-ACT

	Test statistic	*p*-value
All-cause death + CV hospitalization (primary endpoint)	**3.44**	**0.0006**
CV death + CV hospitalization	3.89	<0.001
All-cause death + All cause hospitalization	2.62	0.009

Source: Statistical Reviewer's table

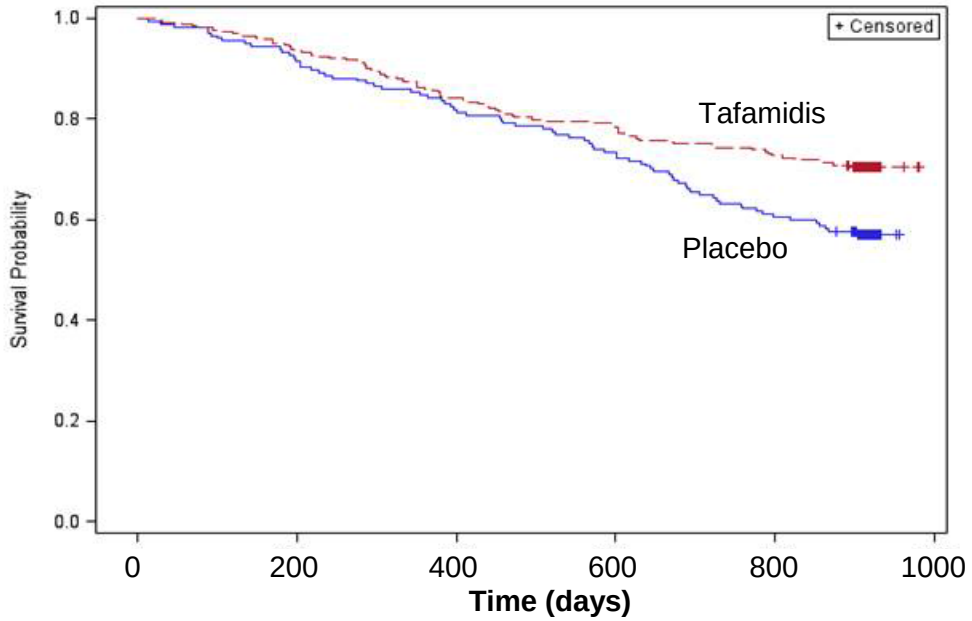
Table 7: Summary of Mortality and Hospitalization in ATTR-ACT

	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Pooled Tafamidis (N=264) n (%)	Placebo (N=177) n (%)
All Subjects:				
Total Deaths[a]	23 (26.1)	49 (27.8)	72 (27.3)	72 (40.7)
CV-related	17 (19.3)	36 (20.5)	53 (20.1)	50 (28.2)
Indeterminate	1 (1.1)	4 (2.3)	5 (1.9)	9 (5.1)
Non-CV-related	5 (5.7)	9 (5.1)	14 (5.3)	13 (7.3)
Total Hospitalized[b]	65 (73.9)	125 (71.0)	190 (72.0)	136 (76.8)
CV-related	42 (47.7)	96 (54.5)	138 (52.3)	107 (60.5)
Indeterminate	1 (1.1)	2 (1.1)	3 (1.1)	0
Non-CV-related	44 (50.0)	81 (46.0)	125 (47.3)	80 (45.2)
Heart Transplants[c]	1 (1.1)	6 (3.4)	7 (2.7)	4 (2.3)
Cardiac Mechanical Assist Device Implantation	0	2 (1.1)	2 (0.8)	0

Source: Applicant's CSR Table 9, verified by Statistical Reviewer
[a] Deaths up to 30 months post-randomization.
[b] Admitted to a hospital during trial; hospitalizations prior to randomization not included. Subjects may be counted for each category of hospitalization that applies.
[c] Includes heart and heart-combo transplantations.

Figure 4 is a Kaplan-Meier (KM) plot of the pooled tafamidis arms vs. placebo for all-cause mortality. The curves start to diverge at about 500 days (~1.5 years). The estimated hazard ratio for all-cause mortality was 0.70 with 95% confidence interval (CI) 0.51, 0.96, and a *p*-value of 0.0259. This difference was driven by cardiovascular death, which accounted for approximately 70% of total deaths in both the pooled tafamidis group and the placebo group.

Figure 4: Kaplan-Meier Plot of All-Cause Mortality in ATTR-ACT – Pooled Tafamidis Arms (N=264) vs. Placebo (N=177)



Source: Statistical Reviewer's Analysis.

The statistical reviewers performed independent analyses of cardiovascular hospitalizations. The pooled tafamidis arms had a lower rate of cardiovascular hospitalization than the placebo arm (Table 8).

Table 8: Cardiovascular Hospitalization Rates in ATTR-ACT

	Pooled Tafamidis	Placebo
Total N	264	177
Total Number of Subjects with CV hospitalization	138 (52.3%)	107 (60.5%)
Average CV hospitalizations during 30 months (per year) among those alive at Month 30	0.297	0.455
Frequency of CV hospitalization per year		
Mean	0.999	0.884
Median	0.395	0.403
Mix, Max	0, 21.49	0, 7.23
Frequency of CV hospitalization per year based on Poisson regression analysis (95% CI)	0.475 (0.418, 0.540)	0.703 (0.617, 0.800)
Relative Risk Ratio based on Poisson regression analysis (95% CI)	0.68 (0.56, 0.81)	

Source: Statistical reviewer's analysis

Thus, data for the primary endpoint and its components, all-cause mortality and cardiovascular hospitalization, favor either dose of tafamidis meglumine over placebo. These results constitute substantial evidence of the efficacy of either tested dose of tafamidis meglumine for reducing the rates of death and cardiovascular hospitalization in patients with ATTR-CM. See Section 11 for a

discussion of concerns regarding [redacted] (b) (4)

Secondary Endpoint Results:
There were two key secondary endpoints in the hierarchical alpha-sparing analytical plan. The first was the 6-Minute Walk Test (6MWT) (change from baseline to Month 30). Mean distance covered in the 6MWT worsened in both treatment groups; however, the decline was statistically significantly greater in the placebo group (a treatment effect of 75.7 meters). Results are shown by subgroups of NYHA Function Class, TTR type, and dose in Table 9. Results are similar for both doses. Mean treatment effect is less in patients who are NYHA Function Class III at baseline.

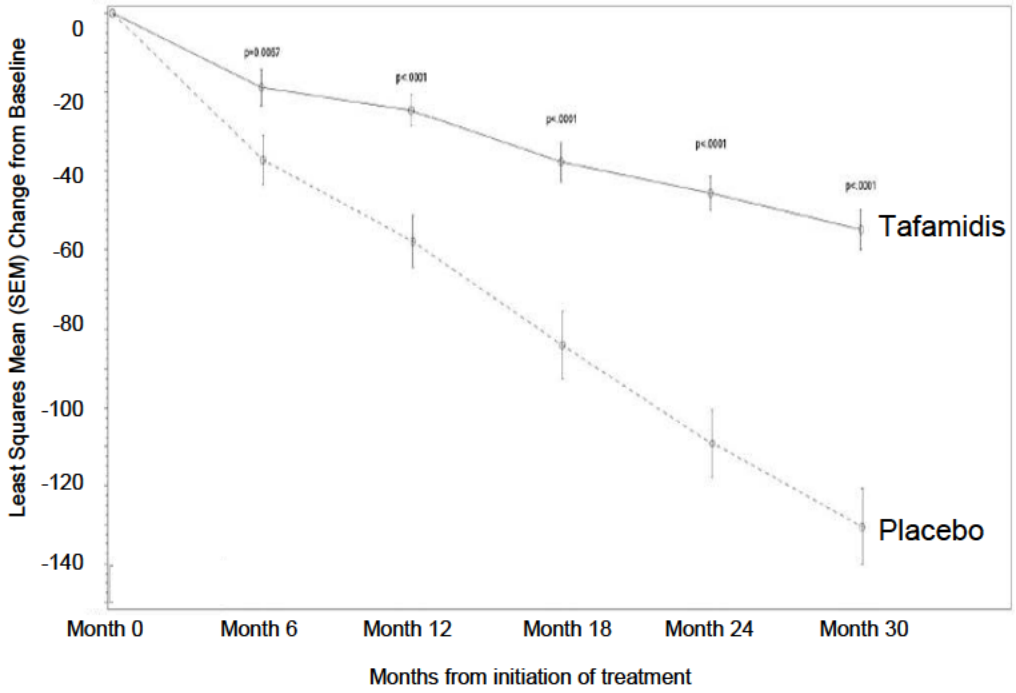
Figure 5 shows the decreases in 6MW distance as a function of time (negative values indicate worsening). Separation of the curves was evident as early as Month 6.

Table 9: 6-Minute Walk Test; Decrease from Baseline at Month 30 (Meters), ITT Analysis

	Tafamidis pooled			Placebo			LS means	95% CI
	N	Mean	STD	N	Mean	STD		
Overall	155	-30.6	87.9	70	-89.7	105.1	75.7	(57.6, 93.8)
NYHA class I or II	132	-27.1	86.3	57	-93.5	110	85.4	(64.1, 106.7)
NYHA class III	23	-50	96.1	13	-72.9	82.1	31.6	(-11.7, 74.8)
TTR wild type	131	-24.4	89.5	62	-89.1	107.2	77.1	(56.0, 98.3)
TTR variant	24	-63.8	71.3	8	-93.9	93.7	79.6	(21.1, 138.1)
80 mg vs placebo	101	-31.2	85.3	70	-89.7	105	75.8	(56.0, 95.6)
20 mg vs placebo	54	-29.1	93.3	70	-89.7	105	75.6	(48.7, 102.5)

Source: Statistical Reviewer's Analysis

Figure 5: 6MWT Change from Baseline to Month 30 in ATTR-ACT (ITT Analysis)



Source: CSR Figure 4.

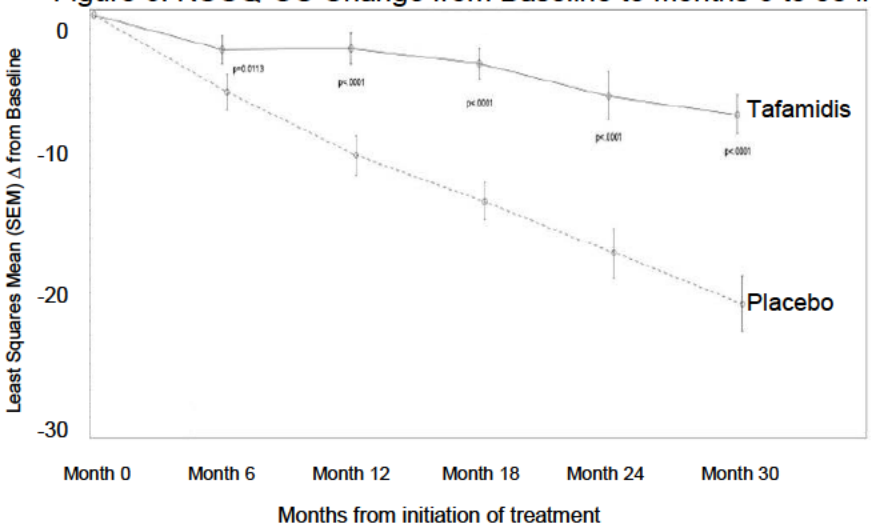
The other key secondary endpoint was the change from baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS). Lower scores correspond to worsening of heart failure symptoms. Results for this endpoint also were statistically significant in favor of the pooled tafamidis treatment arms. Again, the curves diverged as early as Month 6 (Table 10, Figure 6). The two active treatment arms had similar results (Table 10). At 30 months, the difference in changes from baseline for the pooled tafamidis and placebo was 13.7 points, in favor of tafamidis. Treatment effects were similar across all domains of the KCCQ (data not shown). Notably, a 5-point difference in the OS is thought to be "clinically meaningful."[3] Accordingly, the results for the KCCQ-OS support the efficacy of tafamidis in patients with ATTR-CM. For the KCCQ-OS as well as the 6MWT, subjects in all groups showed worsening in their results over the course of the study, but worsening was greater in the placebo arm. Thus, tafamidis meglumine beneficially affected outcomes for both key secondary endpoints in the confirmatory study, and this is reflected in labeling.

Table 10: KCCQ-OS Decrease from Baseline to Month 30 in ATTR-ACT

	Tafamidis pooled			Placebo				
	N	Mean	STD	N	Mean	STD	LS means	95% CI
Overall	170	-3.9	19.3	84	-14.6	21.4	13.7	(9.5, 17.8)
NYHA class I or II	141	-4.3	18	64	-15.1	22.4	13.6	(9.2, 18.0)
NYHA class III	29	-1.7	24.8	20	-13.3	18.2	13.1	(3.3, 22.8)
TTR wild type	140	-4	18.4	74	-13.8	20.7	12.7	(8.6, 16.8)
TTR variant	30	-3.1	23.6	10	-21	26.4	18.2	(3.0, 33.4)
80 mg vs placebo	110	-3.9	19.3	84	-14.6	21.4	13.5	(9.2, 17.8)
20 mg vs placebo	60	-3.8	19.5	84	-14.6	21.4	14	(8.2, 19.8)

Source: Statistical Reviewer's Analysis.

Figure 6: KCCQ-OS Change from Baseline to Months 6 to 30 in ATTR-ACT

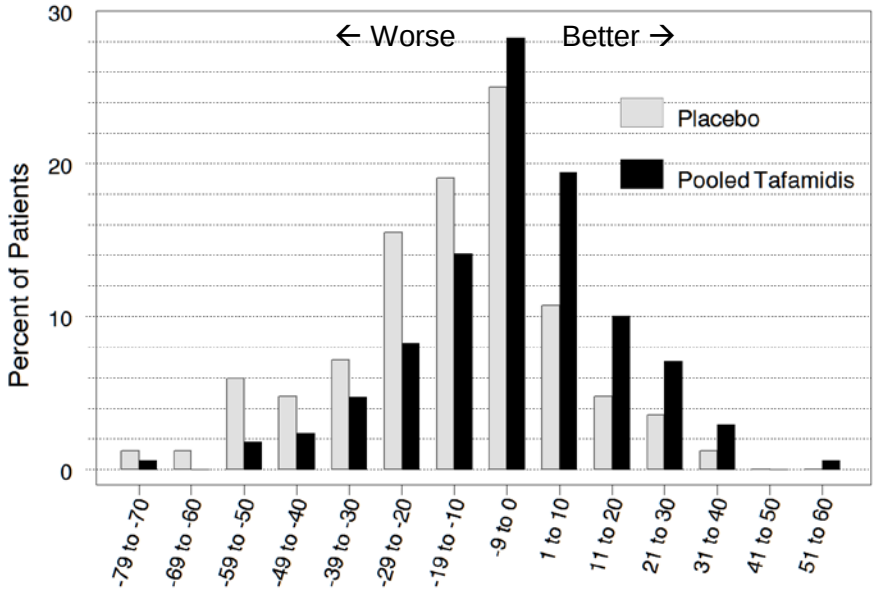


Source: CSR Figure 5

[3] Flynn KE, Lin L, Moe GW, et. al. Relationships Between Changes in Patient-Reported Health Status and Functional Capacity in Outpatients with Heart Failure. *Am Heart J* 2012;163: 88-94.

Figure 7 shows the distribution of changes in KCCQ-OS for the 254 subjects who contributed data at Month 30 in a histogram. The shift to the right (improvement) is evident in the pooled tafamidis group. On average, the bars are higher on the left side of the histogram than on the right side, reflecting overall worsening on all patients.

Figure 7: Distribution in Responses in KCCQ-OS in ATTR-ACT



Data (CHG) plotted from adkccq.xpt by planned treatment group (TRT01P), where AVISIT = Month 30.

NT-proBNP blood concentration was an exploratory endpoint. NT-proBNP blood levels are elevated in patients with heart failure and tend to decrease with effective treatment. In patients with ATTR-CM, NT-proBNP levels tend to be higher than in patients with heart failure due to other causes. Changes in NT-proBNP from baseline to Month 12 or 30 favored tafamidis over placebo.

Financial Disclosures:

Financial disclosure by the investigators in the confirmatory cardiomyopathy study was adequate. The Applicant states that the study was performed in compliance with CGP guidelines.

Choice of the Recommended Dose in Labeling:

As noted above, clinical results for efficacy were similar for tafamidis meglumine 20 mg QD and 80 mg QD in the cardiomyopathy study. Safety results were also similar for the two dose groups (see Section **8**). Thus, consideration of other data is necessary to inform the decision on what dose or doses of tafamidis to recommend in labeling.

There was greater TTR tetramer stabilization at higher doses in a pooled analysis of 11 studies. This biomarker is postulated, but not proven, to be associated with improved clinical outcomes in patients with ATTR-CM, providing weak support for use of the higher dose. The adverse event profiles were similar for the two doses. Considered together, the biomarker and safety data suggest

that the 80 mg dose is preferable to the 20 mg dose for the treatment of ATTR-CM, and perhaps other manifestations of ATTR amyloidosis.

It should be noted that the Division of Cardiovascular and Renal Products often allows use of unvalidated biomarkers in making decisions regarding doses of experimental drugs to be used in clinical trials and sometimes for dosing recommendations in labeling. This does not necessarily imply that changes in these biomarkers could be used as substantial evidence of efficacy to support a drug approval. Currently, the Division does not consider TTR stabilization to be an acceptable surrogate endpoint to establish efficacy in trials of drugs for ATTR-CM and does not consider NT-proBNP to be an acceptable surrogate endpoint to establish efficacy in trials of drugs for any type of heart failure.

8. Safety

ATTR-ACT - Duration of Exposure and Adherence:

The planned exposure in ATTR-ACT was 30 months. Actual median exposure was close to that, at 29.7 and 29.8 months in the tafamidis meglumine 20 mg and 80 mg arms respectively, and 27.9 months in the placebo arm. Table **11** provides summary statistics on exposure and adherence.

Table 11: Exposure and Adherence in the ATTR-ACT Safety Population

	Tafamidis meglumine 20 mg (N=88)	Tafamidis meglumine 80 mg (N=176)	Placebo (N=177)
Exposure Duration (Days)			
Mean (SD)	744 (284)	724 (292)	669 (294)
Median	904	907	850
Min, Max	19, 941	8, 931	14, 930
Dosing Adherence[a]			
n	84	167	177
<80%	3 (3.6%)	3 (1.8%)	5 (3.0%)
≥ 80%	81 (96.4%)	164 (98.2%)	163 (97.0%)
Duration of Treatment (months)			
n	88	176	177
Mean (SD)	24.4 (9.35)	23.8 (9.59)	22.0 (9.66)
Median	29.7	29.8	27.9
Min, Max	0.6, 30.9	0.3, 30.6	0.5, 30.6
Duration Category (months)			
0 to <1	1	4	1
1 to <3	3	3	7
3 to <9	6	14	21
9 to <12	2	11	5
12 to <15	6	9	14
15 to <18	2	5	7
18 to <21	3	8	11
21 to <24	1	3	13
24 to <27	3	1	8
≥ 27	61	118	90

Source: CSR Table 30

[a]Dosing Adherence = number of days dosed divided by the number of days participating in the study for each study visit.

Deaths:

Deaths in ATTR-ACT were a component of the efficacy endpoint and not a safety endpoint. Deaths are discussed in Section 7, Efficacy. The rates of death were lower in both tafamidis arms than in the placebo arm.

Information regarding deaths in the ATTR-ACT open-label extension (OLE) phase is shown in Table 12. All patients in the extension phase received tafamidis meglumine. Those who rolled over from one of the tafamidis arms in the ATTR-ACT randomized study received the same dose as in the randomized phase. Patients who received placebo in the randomized phase were randomized 2:1 to receive tafamidis meglumine 80 mg or 20 mg. The duration of treatment in the extension phase

was up to 30 months or the date of availability of prescription tafamidis in the relevant jurisdiction, whichever happened first.

Table 12: Overall Mortality during the Extension Phase of ATTR-ACT

	Tafamidis 20 mg		Tafamidis 80 mg[c]		Tafamidis 80 vs. 20 mg
	n/N (%)	Event Rate[b]	n/N (%)	Event Rate[b]	Hazard Ratio (95% CI)
Death (all cause)	39/116 (34%)	15.9	71/230 (31%)	14.5	0.9 (0.6,1.3)
Placebo-tafamidis[a]	9/28 (32%)	44.2	10/54 (19%)	24.5	0.6 (0.2, 1.4)
Tafamidis-tafamidis	30/88 (34%)	13.4	61/176 (35%)	13.6	1.0 (0.7, 1.6)

a. Subjects who received placebo in the pivotal study received either tafamidis 20 mg or 80 mg in the extension study
b. Event rate per 100 patient-years
c. A protocol amendment dated 20 July 2018 allowed patients taking tafamidis meglumine 80 mg QD in the extension study to be rolled over to tafamidis free acid 61 mg "where available." This does not confound the interpretation of the data because the dosing regimens produce similar exposure to tafamidis free acid, which is the circulating active moiety of tafamidis meglumine. See Section 5 for additional information.

In subjects who received tafamidis meglumine in the confirmatory trial and continued on the same dose in the OLE (the "tafamidis-tafamidis" data row), the rates of death in the two dosing arms were similar. However, the data in the "placebo-tafamidis" row (patients who received placebo in the randomized phase and then tafamidis in the OLE phase) suggest that there was a lower rate of death in the tafamidis meglumine 80-mg group than in the 20-mg dose group. This trend is not consistent with the much larger experience in the randomized phase of the study, however, where the two dose groups had similar rates of death after starting therapy with tafamidis meglumine.

Serious Adverse Events (SAEs):

In the clinical review, Dr. McDowell states the following about SAEs:

"The proportion of subjects who had treatment emergent SAEs was similar in the three groups with 75%, 75.6% and 79.1% in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively. The most common SAEs were cardiac disorders (e.g., cardiac failure, congestive cardiac failure) which reflect the patient population and underlying disease.

During the assessment of safety signals, it is noted that the frequency of SAEs for accident and injuries SMQ was higher in the tafamidis groups (11.4%) compared to the placebo (5.6%) group. The majority of these SAEs were fall-related injuries such as different types of fracture. This finding along with other related signals from common AEs prompt further evaluation of fall-related AEs (see section 8.4.4.3). There was no other observed meaningful imbalance in SAEs."

Falls are discussed further below.

Discontinuations for Adverse Events:

In the clinical review, Dr. McDowell states the following about discontinuations for adverse events:

"Similar proportions of tafamidis-treated patients and placebo-treated patients discontinued due to an adverse event: 5 (5.7%), 12 (6.8%), and 11 (6.2%) from the tafamidis 20 mg, tafamidis 80 mg, and placebo groups, respectively. Figure 17 shows the time to disposition due to an adverse event; similar curves were observed among the treatment groups. [The figure is not reproduced here.] Requests for dose reductions due to AEs were infrequent and occurred in 4 subjects in the placebo group and 2 subjects (one had headache and the other had urinary tract pain, both coded with moderate severity) in the tafamidis 80 mg group."

Adverse Events of Special Interest:

The Applicant described several adverse events (AEs) of special interest based on findings in the ATTR-PN study and post-marketing experience in jurisdictions where tafamidis meglumine has been approved for treatment of ATTR-PN. Rates of these adverse events of special interest are displayed in Table 13. The definitions for these adverse events of special interest were agreed to by DCRP at the pre-NDA meeting with the Applicant. Frequencies of adverse events of special interest are displayed in Table 13.

Table 13: ATTR-ACT – Frequencies of Adverse Events of Special Interest

AESI (SMQ or HLT or group of PTs)	Tafamidis 20 mg (N = 88) n (%)	Tafamidis 80 mg (N =176) n (%)	Placebo (N = 177) n (%)	Risk Diff (%) T20 mg vs. Placebo	Risk Diff (%) T80 mg vs. Placebo
Identified risk from ATTR-PN studies					
Diarrhea	10 (11.4%)	25 (14.2%)	39 (22.0%)	-10.6	-7.8
Upper abdominal pain	8 (9.1%)	14 (8.0%)	16 (9.0%)	0.1	-1.0
Urinary tract infection	10 (11.4%)	22 (12.5%)	30 (16.9%)	-5.5	-4.4
Vaginal infection	0 (0%)	0 (0%)	0 (0%)	0	0
Important potential risk for ATTR-PN studies					
Hypersensitivity	9 (10.2%)	26 (14.8%)	30 (16.9%)	-6.7	-2.1
Hepatotoxicity	23 (26.1%)	38 (21.6%)	40 (22.6%)	3.5	-1.0
Thyroid dysfunction	6 (6.8%)	16 (9.1%)	19 (10.7%)	-3.9	-1.6
Signals identified from post-marketing					
Cardiac Arrhythmia	29 (33.0%)	66 (37.5%)	68 (38.4%)	-5.4	-0.9
Central Nervous System Neoplasia	0 (0%)	0 (%)	0 (0%)	0	0
Fall, Dizziness, Orthostatic Hypotension	43 (48.9%)	74 (42.0%)	74 (41.8%)	7.1	0.2
Infection-related Events	49 (55.7%)	116 (65.9%)	109 (61.6%)	-5.9	4.3
Pancreatitis	0	1 (0.6%)	0	0	0.6

Urinary and vaginal infections were observed at higher rates with tafamidis meglumine 20 mg than placebo in the ATTR-PN study (discussed below), but there was no signal for either of these events in the CM study.

There is a modest excess of infection-related events in the 80 mg arm in the CM study. Also, the rates of pneumonia adverse events (narrow Standard MedDRA Query [SMQ]) were 5.6, 6.3, and 8.0 per 100 patient-years (PY) in the placebo, 20-, and 80-mg arms, respectively. However, the rates of pneumonia serious adverse events were 4.0, 3.3, and 4.0 per 100 PY in the placebo, 20- and 80-mg arms, respectively, which reduces concerns about the risk of tafamidis-related infections.

Dr. McDowell's review also includes analyses of other safety signals of interest in the cardiomyopathy study.

Fall-Related AEs:

Rates of fall-related AEs and SAEs in the cardiomyopathy study are shown in Table 14.

Table 14: Rates of Fall-related Adverse Events and Serious Adverse Events in ATTR-ACT

	N	Subject-years of exposure	N (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Fall-related AEs						
Placebo	177	284	49 (27.7)	17.3 (12. 8, 22.8)		
Tafamidis Meglumine 20 mg	88	157	29 (33.0)	18.5 (12.4, 26.5)	1.2 (-7.1, 9.5)	1.1 (0.7, 1.7)
Tafamidis Meglumine 80 mg	176	301	53 (30.1)	17.6 (13.2, 23.0)	0.3 (-6.5, 7.1)	1.0 (0.7, 1.5)
Tafamidis 20 mg + 80 mg	264	459	82 (31.1)	17.9 (14.2, 22.2)	0.6 (-5.6, 6.8)	1.0 (0.7, 1.5)
Fall-related SAEs						
Placebo	177	331	9 (5.1)	2.7 (1.2, 5.2)		
Tafamidis Meglumine 20 mg	88	176	10 (11.4)	5.7 (2.7, 10.5)	3.0 (-1.0, 6.9)	2.1 (0.9, 5.2)
Tafamidis Meglumine 80 mg	176	346	20 (11.4)	5.8 (3.5, 8.9)	3.1 (-0.0, 6.2)	2.1 (1.0, 4.7)
Tafamidis 20 mg + 80 mg	264	521	30 (11.4)	5.8 (3.9, 8.2)	3.0 (0.3, 5.8)	2.1 (1.0, 4. 5)

Source: Clinical review, Table 23. Note: Length of exposure differs between the treatment-specific rows for AEs and SAEs because for patients who had a fall-related AE or SAE, the last day of exposure was the day of the event, even if study drug was continued. In patients without events, the last day of exposure was the day of the last dose of study drug. Because there were considerably more AEs than SAEs in each arm, exposure was greater for the SAE analysis because fewer patients had an early cut-off of "exposure."

The three arms were similar in terms of their rates of fall-related AEs, but both tafamidis meglumine arms had about double the rate of fall-related SAEs compared to the placebo arm. Of note, the AE of balance disorder was reported in 2/88 (2.3%), 15/176 (8.5%), and 2/177 (1.1%) of subjects in the 20-, 80-mg, and placebo arms, respectively, suggesting a dose response for this event. However, a mechanistic explanation is lacking. Nonetheless, falls and fall-related events, including balance disorder, merit follow-up in the post-marketing period.

Cataracts and other Lens Disorders:

There were higher rates of lens disorders in both tafamidis meglumine arms than in the placebo arm, based on an analysis of the lens disorder SMQ, which includes the terms cataract, vision blurred, visual impairment and visual acuity reduced (Table 15). There was evidence for a dose response.

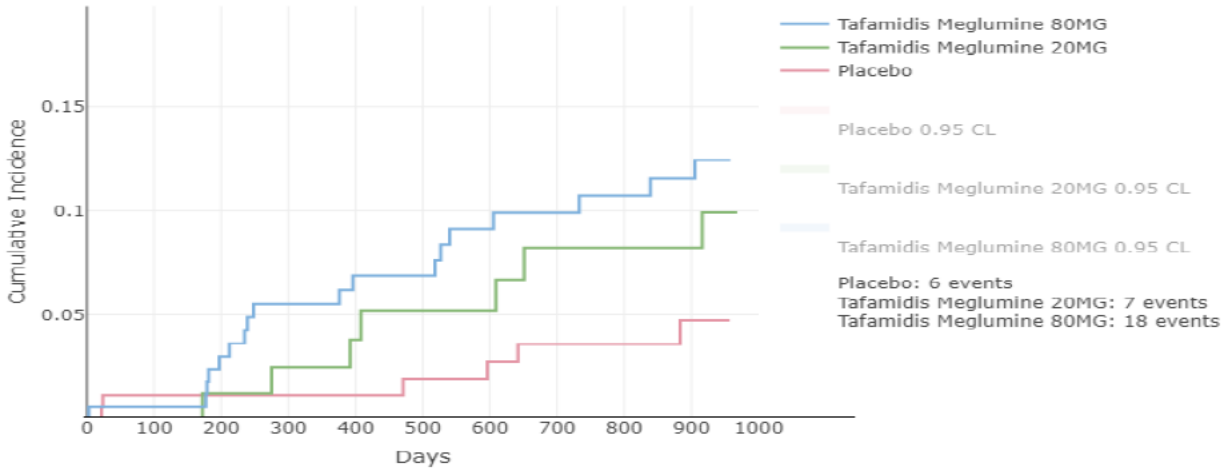
Table 15: Rates of AEs in the Lens Disorder SMQ[a] in ATTR-ACT

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Placebo	177	328	6 (3.4)	1.8 (0.7, 4.0)	-	-
Tafamidis Meglumine 20 mg	88	177	7 (8.0)	4.0 (1.6, 8.2)	2.1 (-1.2, 5.4)	2.2 (0.7, 6. 5)
Tafamidis Meglumine 80 mg	176	341	18 (10.2)	5.3 (3.1, 8.3)	3.5 (0.6, 6.3)	2.9 (1.1, 7.3)
Tafamidis M. 20 mg + 80 mg	264	518	25 (9.5)	4.8 (3.1, 7.1)	3.0 (0.6, 5.4)	2.6 (1.1, 6.4)

[a] includes cataract, vision blurred, visual impairment, visual acuity reduced

Figure 8 shows a KM plot for AEs in the Lens Disorder SMQ over the course of the study.

Figure 8: Kaplan-Meier Plot of AEs in Lens Disorder SMQ in ATTR-ACT



Because of the suggestion of a dose response and the statistically significant finding with the 80-mg dose in the incidence rate ratio analysis, we obtained a consult from the Division of Transplant and Ophthalmology Products. Dr Wiley Chambers was our consultant. Dr. McDowell summarizes his findings as follows:

"Dr. Chambers had reviewed all the reported ophthalmic disorders in the phase 3 ATTR-CM study and re-categorized them as needed. He also evaluated the signals by accounting for cases of cataracts/cataract surgery at baseline. He concluded that the incidence of ocular AEs including cataract development is not believed to be a signal of a drug-related AEs based on the background rate of cataract in the patient population. In addition, there were negative findings in ophthalmic examinations in animals."

Other AEs of Interest:

Liver

Nonclinical studies have shown some tafamidis-associated hepatic alterations at exposures approximately 0.7 times the human exposure at the 80-mg dose of tafamidis meglumine and 2.5-times the human exposure at the 20-mg dose. Although the mechanism for those findings is not clear, hepatotoxicity is considered a potential risk for tafamidis and was an adverse event of special

interest. Using the MedDRA SMQ of drug-related hepatic disorder (narrow scope), there was no imbalance regarding hepatotoxicity-related adverse events.

Table 16 summarizes liver laboratory abnormalities. The three study groups were similar with respect to alkaline phosphatase (ALP) and total bilirubin (TB). For aspartate aminotransferase (AST) and alanine aminotransferase (ALT), the 80-mg group had more abnormalities than the other two groups.

Table 16: Abnormal Liver Laboratory Studies in ATTR-ACT

Liver Lab Test	Tafamidis Meglumine 20 mg N = 88			Tafamidis Meglumine 80 mg N = 176			Placebo N = 177		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	6	5	5.7	8	8	4.6	5	4	2.3
3x ULN	0	0	0.0	4	4	2.3	1	1	0.6
5x ULN	0	0	0.0	3	3	1.7	0	0	0.0
10x ULN	0	0	0.0	1	1	0.6	0	0	0.0
20x ULN	0	0	0.0	1	1	0.6	0	0	0.0
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	3	3	3.4	16	13	7.4	17	8	4.5
3x ULN	1	1	1.1	6	5	2.8	0	0	0.0
5x ULN	0	0	0.0	1	1	0.6	0	0	0.0
10x ULN	0	0	0.0	1	1	0.6	0	0	0.0
20x ULN	0	0	0.0	0	0	0.0	0	0	0.0
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	16	5	5.7	26	11	6.3	63	16	9.0
3x ULN	0	0	0.0	1	1	0.6	6	3	1.7
5x ULN	0	0	0.0	0	0	0.0	0	0	0.0
10x ULN	0	0	0.0	0	0	0.0	0	0	0.0
20x ULN	0	0	0.0	0	0	0.0	0	0	0.0
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	81	22	25.0	133	36	20.5	141	45	25.4
2x ULN	26	10	11.4	44	17	9.7	42	15	8.5
3x ULN	1	1	1.1	3	1	0.6	11	4	2.3

Notes: All reports are post-baseline. Subjects may be counted more than once if they qualify for more than one condition (i.e., 2x, 3x, 5x…) that apply. ULN = upper limit of normal.

Dr. McDowell also analyzed the data for the occurrence of Hy's Law cases. There were two patients who met the criteria for Hy's Law (values of ALT or AST ≥ 3x the upper limit of normal (ULN) and TB ≥ 2x ULN at the same visit). Both were in the 80-mg group.

A 75 year-old white male with NYHA Class III heart failure, atrial fibrillation, and chronic kidney disease met Hy's law criteria 36 days after study entry in connection with a hospitalization for complete AV block and hypotension with pacemaker insertion. The patient was discharged after 5 days. Laboratory abnormalities had resolved by Day 102, the next time they were measured. The

patient continued on tafamidis for about 2 years and his liver enzymes were within the normal range.

A 74 year-old black male with Class III HF and a history of chronic obstructive pulmonary disease (COPD) developed elevated liver studies with worsening COPD on study day 464. The liver function values were considered to be resolved, although no additional values are in the record. He discontinued therapy one month later (study day 496) because of worsening dyspnea. He died about one year later with end-stage COPD.

In the view of the review team, neither of these cases was consistent with drug-induced liver injury. For the first subject, the abnormalities were likely due to AV block complicated by hypotension. For the second subject, ALT and AST were normal during treatment for more than 1 year and the liver abnormalities occurred at the last visit when the subject also experienced worsening dyspnea, heart failure, and an exacerbation of COPD. It is likely that the event was secondary to cardiac decompensation.

A third subject, an 82 year-old black male (also in the 80 mg arm), developed both ALT and AST > 10 x ULN on study day 8. He was hospitalized the next day and study drug was permanently discontinued. He had a coronary angioplasty on study day 12. He died on study day 38 due to "cardiomyopathy." Of note, all of his Day 1 liver function studies (drawn before his first dose of study drug) were substantially increased over his screening values, suggesting an insult that predated the initiation of the study drug, possibly ischemic hepatitis secondary to heart failure. One cannot rule out a contribution of study drug to his worsening state after Day 1. See summary table below:

Subject's Liver Function Studies

	Screening	Day 1	Day 8
ALT	54	124	866
AST	46	111	714
ALP	76	132	115
BILI	1	1.6	1.6
GGT	56	89	74

As explained in the clinical review, assessing hepatotoxicity in ATTR-CM patients is challenging because elevated transaminases can be confounded by patients' cardiovascular disease. Given the totality of data available to date, there is insufficient evidence to establish a causal relationship between tafamidis and hepatotoxicity, but hepatotoxicity remains a potential risk.

Hypothyroidism

Tafamidis interferes with binding of thyroid hormone to ATTR. In ATTR-ACT, there were dose-dependent decreases in T4 and, to a lesser extent, free T4 in the tafamidis groups starting at Week 2 and continuing throughout the study. There were no meaningful changes in TSH or retinol-binding protein (RBP) across time in the study, which strongly suggests that the binding is not clinically important. Of note, analysis of the thyroid dysfunction SMQ and the "Asthenic condition" MedDRA HLT revealed no signals. Finally, concomitant medication use for hypothyroidism in the phase 3 study was also evaluated. Dr. McDowell stated in her review,

Reference ID: 4428559

"There were 13.6%, 23%, and 18% of subjects who used levothyroxine, iodine, and/or liothyronine in the trial in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively. However, the baseline uses of these medications was slightly imbalanced: 8%, 17% and 12% in the tafamidis 20 mg, tafamidis 80mg and placebo groups, respectively. After taking account for the baseline use, the percentage of subjects who started medication for hypothyroidism in the study was similar with 8.2%, 6.2% and 6.5% in the tafamidis 80 mg, tafamidis 20 mg and placebo groups, respectively."

There is not enough evidence here to support labeling warning/precaution regarding thyroid abnormalities. We will, however, look for more evidence during marketing.

Treatment Emergent AEs (TEAs) and Adverse Drug Reactions (ADRs):

Predefined adverse events of special interest, based on previous trials and post-marketing data, have been discussed (Table 13). No pre-existing signals were confirmed. Table 17 shows the overall incidence of treatment-emergent adverse events of various broad categories in the study arms. There are no differences among the study arms.

We have not yet identified any adverse drug reactions for labeling; however, the Office of Surveillance and Epidemiology (OSE) will be alerted to follow adverse events related to hypothyroidism and falls or balance disorders post-marketing.

Table 17: Incidence of Treatment-emergent Adverse Events in ATTR-ACT

Treatment-Emergent Adverse Events - By Dose and Pooled Active Treatment				
	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
	n (%)	n (%)	n (%)	n (%)
Treatment-emergent AEs (all causalities)				
Patients with TEAEs	87 (98.9)	173 (98.3)	260 (98.5)	175 (98.9)
Patients with treatment-emergent SAEs	66 (75.0)	133 (75.6)	199 (75.4)	140 (79.1)
Patients with severe TEAEs	54 (61.4)	110 (62.5)	164 (62.1)	114 (64.4)

Other Laboratory Studies:

Dr. McDowell plotted mean values of RBP over the course of the study (Figure 22 in the Clinical review). Like thyroxine, RBP binds to ATTR. Compared to the placebo arm, in which RBP concentration in blood values were stable at about 5 mg/dL, mean RBP values in the 80 mg arm fell about 10% by Month 1 and remained similarly reduced over the course of the study. Conversely, RBP values in the 20-mg arm increased by about 5% relative to the placebo group. The clinical implications of these changes are unclear.

9. Advisory Committee Meeting

The applications for tafamidis meglumine and tafamidis were not referred to an FDA advisory committee because these applications did not raise significant public health questions on the role of the drugs in the diagnosis, cure, mitigation, treatment, or prevention of ATTR-CM. The application clearly provides substantial evidence of effectiveness, and there were no critical safety issues. In short, outside expertise was not deemed necessary to assist in our decision-making for these NDAs.

10. Pediatrics

ATTR-CM and PN are diseases of adults that are rarely diagnosed in children, although there was a recent report of hATTR-PN in a 13 year-old in an affected family, and a few cases in older teenagers have been described in the literature. It would be difficult to study symptomatic pediatric patients in a rigorous way. It might be possible to treat asymptomatic children with known genetic defects leading to these conditions to prevent or delay the onset of clinically evident illness. However, clinical trials to evaluate such use would require years of follow-up, might be slow to fully enroll, and might not be feasible for even the largest and most patient of pharmaceutical companies. In any case, because this indication has orphan drug designation, the Applicant is exempt from required pediatric assessments.

11. Other Relevant Regulatory Issues

Substantial Evidence of Effectiveness:

Substantial evidence of effectiveness is generally understood to mean two independent adequate and well controlled studies, each convincing on its own. FDA's 1998 Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," describes situations in which a single adequate and well-controlled multicenter study may provide evidence of effectiveness without supporting information from other adequate and well-controlled studies. The Guidance goes on to identify characteristics of such a study that could lead to a conclusion that the single study is capable of supporting an effectiveness claim.

ATTR-ACT has most of the characteristics described in the Guidance. ATTR-ACT was a large multicenter study in which: 1) no single study site provided an unusually large fraction of the patients; 2) no single site or investigator was disproportionately responsible for the favorable treatment effect; 3) the results were consistent across demographic and disease-specific subsets; 4) the study included several important and prospectively identified endpoints, each of which represented beneficial, yet different, effects (survival, freedom from hospitalization, symptoms, and exercise performance); and 5) the *p*-value is persuasive, i.e., highly inconsistent with the null hypothesis. Finally, in light of the improved survival shown in ATTR-ACT, it would be difficult or impossible to perform a second study on ethical grounds.

For all the above reasons, it is clear that ATTR-ACT, as a single adequate and well controlled study, is sufficient to provide evidence of effectiveness without supporting information from a second study.

Labeling Claims:

When the two NDAs under review here were initially submitted to DCRP in 2018, the Applicant sought (b) (4)

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(b) (4)

Indication Statement for Cardiomyopathy:

The Applicant (b) (4) Findings for "all-cause" mortality will be described in Section 14 of labeling because that was a component of the pre-specified primary endpoint, (b) (4)

12. Labeling

We have reached agreement with the Applicant on labeling.

13. Postmarketing Recommendations

We have agreed with the Applicant regarding creation of a pregnancy registry. No additional post-marketing studies are recommended. We will ask the Office of Surveillance and Epidemiology to follow several safety issues post-marketing, including events related to hypothyroidism and those related to falls and balance disorders.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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