CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211996Orig1s000 212161Orig1s000

CLINICAL REVIEW(S)

Clinical Review

Application Type	NDA
Application Number(s)	212161
Priority or Standard	Standard
Submit Date(s)	November 2, 2018
Received Date(s)	November 2, 2018
PDUFA Goal Date	November 2, 2019
Division/Office	DCaRP/ODE-1
Reviewer Name(s)	Preston Dunnmon, MD Tzu-Yun McDowell, PhD
Review Completion Date	April 5, 2019
Established/Proper Name	Tafamidis
(Proposed) Trade Name	Vyndamax
Applicant	Pfizer
Dosage Form(s)	61 mg free acid capsule
Applicant Proposed Dosing Regimen(s)	61 mg once daily (QD) A single tafamidis 61 mg capsule is bioequivalent to tafamidis meglumine 80 mg (four 20 mg tafamidis meglumine capsules) and is not interchangeable on a per mg basis
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Vyndamax is indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce (b) (4) [redacted] cardiovascular-related hospitalization (b) (4) [redacted]

Executive Summary

NDA 212161 was submitted in parallel with NDA 211996 (tafamidis meglumine) on 02 November 2018, which contains primarily the CMC information supporting the tafamidis 61 mg free acid capsule. The bioequivalence/bioavailability studies demonstrating the equivalence of tafamidis 61 mg free acid with 80 mg (4x 20 mg) tafamidis meglumine dose were included in NDA 211996 and reviewed by the Office of Clinical Pharmacology. The tafamidis free acid 61 mg oral capsule formulation is found to be therapeutically equivalent to tafamidis meglumine 80 mg oral capsule. The clinical efficacy and safety data supporting the approval of tafamidis free acids 61 mg (NDA 212161) can be cross-referencing the clinical review of tafamidis meglumine NDA 211996.

The applicant also provided additional data to support the safety of tafamidis 61 mg for treatment of patients with ATTR-CM in the 120-Day Safety Update on April 2nd, 2019. This new safety data contains a total of 87 ATTR-CM patients who were exposed to tafamidis 61 mg free acid as of the data cutoff date of 15 January 2019. The median duration of the treatment was about 3 months. No new safety signals or concerns were identified from this short-term data. Overall, this updated safety information does not change the benefit-risk profile of tafamidis free acid 61 mg (referenced to tafamidis meglumine 80 mg in NDA 211996). We recommend the approval of NDA 212161.

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/s/

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CLINICAL REVIEW

Application Type	NDA
Application Number(s)	211996
Priority or Standard	Priority
Submit Date(s)	November 2, 2018
Received Date(s)	November 2, 2018
PDUFA Goal Date	July 2, 2019
Division/Office	DCaRP/ODE-1
Reviewer Name(s)	Preston Dunnmon, MD Tzu-Yun McDowell, PhD
Review Completion Date	March 28, 2019
Established/Proper Name	Tafamidis meglumine
(Proposed) Trade Name	Vyndaqel
Applicant	Pfizer
Dosage Form(s)	20 mg (b) (4)
Applicant Proposed Dosing Regimen(s)	80 mg once daily (QD)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Vyndaqel is indicated for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce (b) (4) cardiovascular-related hospitalization (b) (4)

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Glossary

6MWT	6-Minute Walk Test
AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR	adverse reaction
AST	aspartate aminotransferase
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
BCRP	Breast Cancer Resistance Protein
BL	baseline
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMAD	cardiac mechanical assist device
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	Clinical Outcome Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	Cardiovascular

DCRP	Division of Cardiovascular and Renal Products
DMC	data monitoring committee
DPMH	Division of Pediatric and Maternal Health
DTOP	Division of Transplant and Ophthalmology Products
EAC	endpoint adjudication committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FOI	fraction of initial
FS	Finkelstein-Schoenfeld
GCP	good clinical practice
GRMP	good review management practice
hATTR-CM	hereditary (variant) transthyretin amyloid cardiomyopathy
HF	heart failure
HV	healthy volunteer
ICD	informed consent document
ICH	International Council for Harmonization
IEC	Independent Ethics Committee(s)
IND	Investigational New Drug Application
IRB	Institutional Review Board(s)
IRT	Interactive Response Technology system
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire-Overall Summary Score
KCCQ-PL	Kansas City Cardiomyopathy Questionnaire- Physical Limitation Score
KCCQ-TS	Kansas City Cardiomyopathy Questionnaire- Total Symptom Score
K-M	Kaplan-Meier
M	molar
M/M	molar ratio
mBMI	modified body mass index (BMI kg/m^2) x (serum albumin g/L)
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
mITT	modified intent to treat

MMRM	mixed model repeated measures
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NIS-LL	Neuropathy Impairment Score of the Lower Limb
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QOL-DN	quality of life – diabetic nephropathy
RBP	retinol binding protein
REMS	risk evaluation and mitigation strategy
RMP	risk management plan
ROMI	release of medical information
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	standardized MedDRA query
SOC	standard of care
SOC	systemic organ class
SPA	special protocol agreement
T4	total thyroxine
TB	total bilirubin
TEAE	treatment emergent adverse event
TESPO	Tafamidis Enhanced Surveillance Pregnancy Outcomes (Program)
THAOS	Transthyretin-Associated Amyloidosis Outcome Survey
TQOL	total quality of life

Transthyretin	TTR
TSH	thyroid stimulating hormone
TTRR	tafamidis vs TTR molar ratio(M/M)
ULN	upper limit of normal
United States	US
wtATTR-CM	wild-type transthyretin amyloid cardiomyopathy

1. Executive Summary

1.1. Product Introduction

Tafamidis meglumine (Vyndaqel) is a new molecular entity (NME), small molecule stabilizer of the transthyretin (TTR) tetramer that prevents TTR from dissociating into amyloidogenic monomers, which in turn prevents the deposition of these monomers into the heart and peripheral nerves and the consequent development of transthyretin amyloidosis (ATTR) involving these tissues. The applicant proposes the following (b) (4)

(b) (4)

The 20mg capsule of tafamidis meglumine taken once daily was approved in the European Union (EU) in 2011 "for the treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment" on the basis of ATTR-PN Study B3461020 (Fx-005). Tafamidis meglumine 20 mg capsules are now approved in 41 countries for the treatment of ATTR-PN.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has demonstrated substantial evidence of effectiveness, including reduction in all-cause mortality, reduction of the frequency of cardiovascular hospitalizations, improved functional capacity, and improved quality of life in a rigorously conducted, adequately sized study with two doses of active drug (study B3461028). The design of this study incorporated input from the Division of Cardiovascular and Renal Products (DCaRP) that resulted in a Special Protocol Agreement (SPA) and prospective concurrence with the statistical analysis plan. In phase 3 development, the frequency of adverse events out to 30 months in patients treated with tafamidis meglumine 20 mg or 80 mg (administered as four 20 mg capsules) was similar to placebo. Transthyretin amyloid cardiomyopathy is a progressive, fatal disease with no approved therapies in the United States.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressively debilitating and ultimately fatal disease. Overall, the median survival for patients with hereditary (variant) 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 transthyretin amyloid cardiomyopathy (wtATTR-CM) is reported to be 3.6 years.[1,2] As the disease progresses, affected patients vacillate between left ventricular filling pressures that are too high (causing pulmonary congestion with shortness of breath and dyspnea on exertion) and left ventricular filling pressures that are too low (causing dizziness and syncope), all on a background of chronic right ventricular failure (causing peripheral, gastrointestinal, and hepatic congestion/edema). (b) (4) In ATTR-CM patients, tafamidis meglumine therapy improves quality of life, increases functional capacity, decreases hospitalization frequency, and decreases all-cause mortality. (b) (4)

[1] Meurer S, Schwartz JH, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. NEJM 2018;379(11):1007-1016.
[2] Grogan, M, Scott CG, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. JACC; 68(10):1015-1020

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	(b) (4) • High mortality rate, especially for symptomatic ATTR-CM	ATTR-CM is a progressively debilitating and ultimately fatal disease. Overall, the median survival for patients with hereditary (variant) 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	• None	There are no approved therapies for ATTR-CM in the United States
Benefit	• For ATTR-CM (wild-type and hereditary) ○ Reduced Mortality ○ Reduced Cardiovascular (CV) hospitalization frequency ○ Improved functional capacity ○ Improved quality of life (b) (4)	For the pooled tafamidis group in the phase 3 pivotal study B3461028 of ATTR-CM, the primary endpoint composite of all-cause mortality (ACM) and CV hospitalization at month 30 was significantly reduced compared to placebo in the Finkelstein-Schoenfeld (FS) ranked analysis with p=0.0006. The Kaplan-Meier analysis of ACM at month 30 demonstrated a hazard ration of HR = 0.65 (0.45, 0.93), a 35% risk reduction. The relative

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		risk ratio of CV hospitalizations per year based on Poisson regression analysis was 0.676 (0.564, 0.811). Patient functional capacity significantly improved by 75.7 (57.6, 93.8) meters on the 6-minute walk test (6MWT). Patient quality of life significantly improved by 13.7 (9.5, 17.8) points on the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OS), with nominally significant improvements in both the KCCQ Total Symptom Score (KCCQ-TS) and KCCQ Physical Limitation Score (KCCQ-PL). (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		(b) (4)
Risk and Risk Management	• Benign overall safety profile • Risk Management for important potential risk ○ Reproductive and developmental toxicity ▪ The potential risk will be addressed in section 8 of labeling ▪ Post-marketing requirements: Establish a prospective, (b) (4) observational study in women exposed to tafamidis during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate ○ Hepatoxicity ▪ Monitor potential hepatic events through pharmacovigilance in the post-marketing setting ○ Thyroid dysfunction ▪ Monitor potential events regarding thyroid dysfunction through pharmacovigilance in the post-marketing setting	In the phase 3 placebo-controlled ATTR-CM clinical trial, the frequency of adverse events out to 30 months in patients treated with tafamidis meglumine 20 mg or 80 mg (administered as four 20 mg capsules) was similar to placebo. Tafamidis is associated with a potential risk of reproductive and developmental toxicity based on animal data. There is limited human data with tafamidis exposure during pregnancy and the risk remains unknow. Pregnant women should be advised on the potential risk for a fetus and breastfeeding is not recommended during treatment with tafamidis. There is also a need to collect long-term safety data on pregnancy outcomes in women exposed to tafamidis during pregnancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Fall ▪ Monitor fall-related events through pharmacovigilance in the post-marketing setting	In the phase 3 study in patients with ATTR-CM, elevated transaminases were observed rarely but more frequently in the tafamidis 80 mg group compared to the placebo group. Tafamidis is also associated with a decrease in serum concentrations of total thyroxine without an accompanying change in thyroid stimulating hormone. However, no corresponding clinical findings consistent with these laboratory abnormalities have been observed. In the phase 3 study in patients with ATTR-CM, although there was no imbalance in fall-related adverse events among the treatment groups, higher incidence of fall-related serious adverse events was observed in both tafamidis groups compared to the placebo group (11.4% vs. 5.1%). Considering the background rate of fall in elderly, no clear mechanisms (e.g. no signal for hypotension or postural hypotension), as well as no signal found in the ATTR-PN program, the totality of data to date is limited to conclude the association between tafamidis and fall. Nevertheless, falls in this patient

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		population could result in devastating outcomes and should be considered as a potential risk and tracked in the post-marketing setting.

1.4. Patient Experience Data

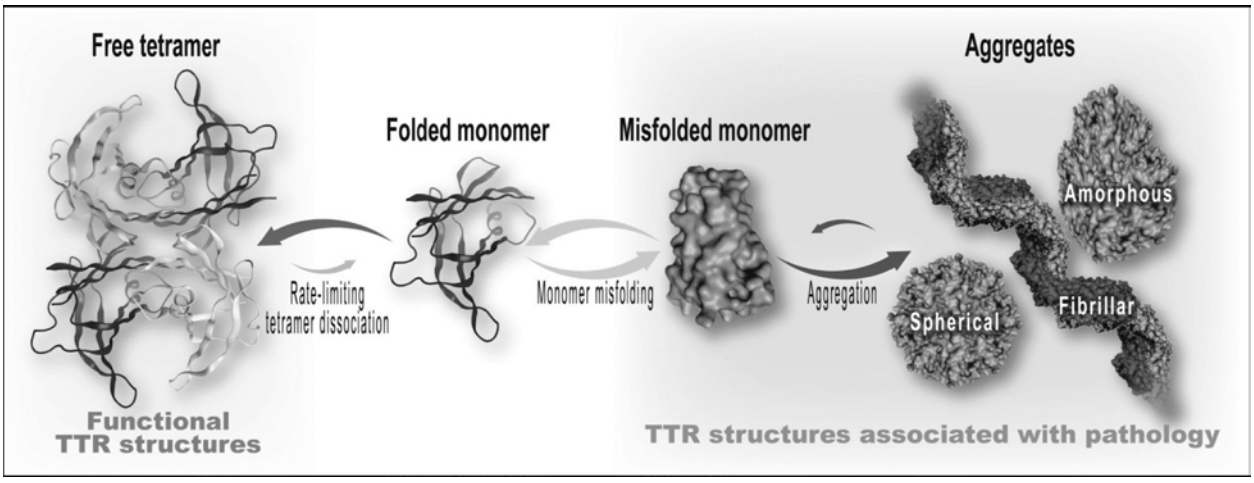
Table 1 Patient Experience Data Relevant to NDA 211996

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		X	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	X	Natural history studies		(b) (4)
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disease for which there are no approved therapies in the United States. This is a deposition disease whereby transthyretin homo-tetramers disassociate into monomeric components, become misfolded, and are deposited into tissues to which they are toxic, according to the diagram below:[3]



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. Alternatively, genetically normal individuals with a normal TTR primary sequence can experience monomeric misfolding due to multiple epigenetic factors.

The transthyretin tetramer has two thyroxine (T4) binding sites, for which it is a minor carrier. Tafamidis 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

[3] Dharmarajan K, Maurer MS. Transthyretin Cardiac Amyloidoses in Older North Americans. J Am Geriatr Soc. 2012 April;60(4):765–774.

of the T4 binding sites is unclear. This is a consideration relevant to maternal-fetal health, in that the body 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.

Transthyretin amyloidosis is the clinical consequence of the deposition of misfolded monomers (or oligomers of those misfolded monomers) in tissues to which they are toxic. The five tissue types involved most commonly are heart, peripheral nerves, central nervous system (CNS), kidney, and eye (vitreous), with ATTR-CM and ATTR-PN accounting for the vast majority of the clinical pathology. These conditions are not mutually exclusive, with reports of as many as 40% of subjects having both cardiac and peripheral neurological manifestations. Tafamidis does not substantially cross the blood-brain-barrier or the blood-retinal-barrier.[4] Therefore, there is no basis to anticipate benefit from tafamidis therapy for ATTR involving the vitreous or central nervous system, since these locations intrinsically produce TTR.

2.2. Analysis of Current Treatment Options

There are no therapies for either hereditary (variant) transthyretin amyloid cardiomyopathy (hATTR-CM) or wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) approved in the United States, and none to date that have been reliably available outside of clinical trials. Pfizer is making tafamidis meglumine available to patients under an expanded access program pending the review if this application.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tafamidis is an NME that is not currently marketed in the United States (US). The result of its prior development for the ATTR-PN indication under new drug application (NDA) 202737 is summarized as follows:

- June 2012: Reflecting the recommendation of its advisory committee, the FDA's Division of Neurology Products issued a Complete Response Letter to the applicant for the ATTR-PN indication (b) (4)

[4] Pfizer slide deck for 02/19/2019 mid-cycle teleconference

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

For the ATTR-CM indication developed under IND 71880, the pertinent regulatory history is as follows:

- February 2012: Orphan drug designation was granted (12-3633) for ATTR-CM to reduce cardiovascular CV hospitalization and CV mortality.
- (b) (4)
- October 2013: Special Protocol Agreement (SPA) Letter issued for protocol B3461028
- November 2013: SPA Modification Agreement Letter issued for protocol B3461028
- Jul 2014: SPA Modification Agreement Letter issued for protocol B3461028 Amendment 1
- Jun 2015: SPA Modification Agreement Letter issued for protocol B3461028 Amendment 2
- Aug 2016: SPA Modification Agreement Letter issued for protocol B3461028 Amendment 3
- May 2017: Fast Track granted
- May 2018: Breakthrough Therapy Designation granted
- August 2018: DCaRP support for Priority Review communicated to applicant.

3.3. Foreign Regulatory Actions and Marketing History

The 20mg capsule of Tafamidis meglumine taken once daily received marketing authorization in the European Union (EU) in 2011 "for the treatment of TTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment" on the basis of ATTR-PN Study B3461020 (Fx-005), and this authorization was renewed in 2016. Tafamidis meglumine 20 mg capsules are now approved in 41 countries for the treatment of ATTR-PN.

The current EMA Summary of Product Characteristics for Vyndaqel 20 mg soft capsules includes the following pertinent information:

- Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.
- The recommended dose of tafamidis meglumine is 20 mg orally once daily.
- No dosage adjustment is required for elderly patients (≥ 65 years).
- No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Tafamidis meglumine has not been studied in patients with severe hepatic

impairment and caution is recommended.
- Women of childbearing potential should use appropriate contraception when taking tafamidis meglumine and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis meglumine.
- As there are no data available regarding the use of tafamidis meglumine post-liver transplantation, tafamidis meglumine should be discontinued in patients who undergo liver transplantation.
- Vyndaqel contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.
- On the basis of the pharmacodynamic and pharmacokinetic profile, tafamidis meglumine is believed to have no or negligible influence on the ability to drive or use machines.
- No cases of acute overdose have been reported. In clinical trials of healthy volunteers, the highest dose of tafamidis given was 480 mg in a single dose and 60 mg once daily for two weeks. The reported treatment-related adverse events were mild to moderate and included: headache, somnolence, myalgia, insomnia, hordeolum, photosensitivity reaction, and presyncope.
- Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, fertility and early embryonic development, genotoxicity and carcinogenic potential.
- In the rat peri- and post-natal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal treatment during pregnancy and lactation at doses of 15 and 30 mg/kg. Decreased fetal weights in males were associated with delayed sexual maturation (preputial separation) and impaired performance in a water-maze test for learning and memory. The NOAEL for viability and growth in the F1 generation offspring following maternal treatment during pregnancy and lactation with tafamidis was 5 mg/kg (HED=0.8 mg/kg), a dose approximately 4.6-times the recommended dose.

The most recent DSUR submitted to date (cutoff 30 October 2018) includes the following pertinent information:

- Urinary tract infection, upper abdominal pain, diarrhea, and vaginal infections are important identified risks for tafamidis. Hepatotoxicity, hypersensitivity reactions, reproductive toxicity and lactation, and changes in thyroid function, particularly in pregnant women, are important potential risks. No new important identified or potential risks related to tafamidis treatment were identified during the reporting period.
- No significant safety information was received after the data lock point of this DSUR.
- There were no actions taken regarding tafamidis for safety reasons by either a health authority (HA) or by the Sponsor during this reporting period.
- As part of Risk Management Plan (RMP) update in December 2018, the proposed list of

safety concerns (important identified risks, important potential risks, and missing information) are summarized below:

Important identified risks	None
Important potential risks	None
Missing information	Patients with NYHA Class IV (ATTR-CM indication)
	Patients with severe renal impairment
	Use in Pregnancy and Lactation

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

None. No audits or site inspections were requested. No data integrity issues were identified. There were no issues with human subject protection.

4.2. Product Quality

None.

4.3. Clinical Microbiology

None.

4.4. Nonclinical Pharmacology/Toxicology

None.

4.5. Clinical Pharmacology

In vitro drug-transporter inhibition study (XT128402) demonstrates that tafamidis has the potential to inhibit Breast Cancer Resistance Protein (BCRP) both systemically and in the gastro-intestinal (GI) tract and may increase the exposure of BCRP substrates. A clinical study has not been conducted to date to characterize this interaction in vivo. If approved, the sponsor will be required to conduct a post-market clinical drug interaction study to evaluate the potential interaction between tafamidis and a relevant BCRP substrate.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

None.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Listing of Clinical Trials Relevant to NDA 211996

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
B3461028		Phase 3, multicenter, international, 3-arm, parallel design, double-Blind, placebo-Controlled, randomized study	Tafamidis 20 mg QD or 80 mg QD orally, or matching placebo	All- cause mortality and frequency of cardiovascular related hospitalizations over the duration of the trial, which is defined as the number of times a subject is hospitalized (i.e. admitted to a hospital) for cardiovascular related morbidity	30 months	441	Subjects Diagnosed with Transthyretin Cardiomyopathy (ATTR-CM)	60 sites; Belgium, Brazil, Canada, Czech Republic, Spain, France, Greece, Italy, Japan, Netherlands, Sweden, Great Britain, United States
		Studies to Support Safety						

B3461045		Phase 3, double- blind randomized, long-term extension to Study B3461028	Tafamidis 20 or 80 mg QD	Safety as measured by all-cause mortality and incidence of treatment-emergent adverse events	Up to 60 months or until local availability of tafamidis by prescription for ATTRCM indication is achieved	330 planned 252 enrolled	ATTR-CM (either genetic variants or wildtype)	41 sites; Belgium, Brazil, Canada, Czech Republic, Spain, France, Germany, Italy, Japan, Netherlands, Sweden, Great Britain, United States
B3461025		Phase 2, open-label, single-arm study	Tafamidis 20 mg QD	TTR stabilization as primary pharmacodynamic endpoint Safety and tolerability were assessed at each study visit	12 months	40 planned 35 enrolled	ATTR-CM (either genetic variants or wildtype)	6 sites in United States
B3461026		Phase 2, open-label, single-arm, long-term extension to study B3461025	Tafamidis 20 mg QD	Safety as measured by all-cause mortality and incidence of treatment-emergent adverse events	Up to 3 years	31	ATTR-CM (either genetic variants or wildtype)	6 sites in United States

		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
B3461009		Randomized, double-blind, placebo-controlled	n=9 (1×20mg, tafamidis) n=9 (40mg tafamidis); n=3 placebo	PD endpoints included TTR plasma concentration and TTR stabilization for predose, time of maximum observed concentration (T_{max}), and 24 hours	Single dose	21 (18 tafamidis, 3 placebo) enrolled	Healthy subjects	1 center in United States
B3461040		Randomized, double-blind, crossover	Tafamidis 240, 350, and 480 mg; Placebo	Safety and tolerability of escalating doses >120 mg of tafamidis. To evaluate the pharmacokinetics and pharmacodynamic stabilization effect TTR	Single dose	9 males 31.2 years (24 to 54)	Healthy subjects	1 center in Singapore
PMAR-EQDD-B346b-DP4-808		PK-PD analysis of tafamidis effect on transthyretin stabilization	N/A	• To explore the relationship between stabilization of transthyretin tetramers and tafamidis concentrations (molar ratio to transthyretin)		771 subjects: 102 healthy volunteers, 152 patients with ATTR-PN (20 Non-Val30Met), and 406 patients	102 healthy volunteers, 152 patients with ATTR-PN (20 Non-Val30Met), and 406 patients with ATTR-CM (340 wild type)	11 clinical studies: 5 Phase 1; 6 Phase 2 /3

				• To evaluate the impact of covariates on the relationship between transthyretin stabilization and tafamidis concentrations (molar ratio to transthyretin) • To assess the time to onset or attenuation of the tafamidis effect on stabilization of transthyretin		with ATTR-CM (340 wild type)		
PMAR-EQDD-B346b-DP4-808 ADDENDUM	Correction of methodology to calculate TTR stabilization. As part of the methodology to calculate TTR stabilization, transthyretin concentrations are measured twice, once before and once after a denaturation step. The independent variable in the PK-TTR analysis is the molar ratio of tafamidis:TTR. The appropriate TTR concentration for this calculation is the pre-denaturation TTR concentration. The error that occurred was that post-denaturation TTR concentrations in Study B3461028 only, were utilized for the molar ratio calculation. The remaining 10 studies in the dataset used pre-denaturation values to calculate TTRR.							

5.2. Review Strategy

Study B3461028 is a relatively large, single, controlled trial supporting this application for the ATTR-CM indication. Its open-label extension, Study B3461045 will be evaluated for safety as well as for the occurrence of mortality in the various groups that will be enrolled (placebo to 20mg tafamidis, placebo to 80 mg, 20 mg to 20 mg tafamidis, 80 mg to 20 mg, 80 mg to 80 mg). Naïve subjects with ATTR-CM who did not participate in the double-blind phase of the trial to were also be randomized to either 20mg or 80 mg tafamidis, and their safety outcomes will also be reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A multicenter, international, phase 3, double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety, and tolerability of daily oral dosing of tafamidis meglumine (PF-06291826) 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy (Study B3461028)

6.1.1. Study Design

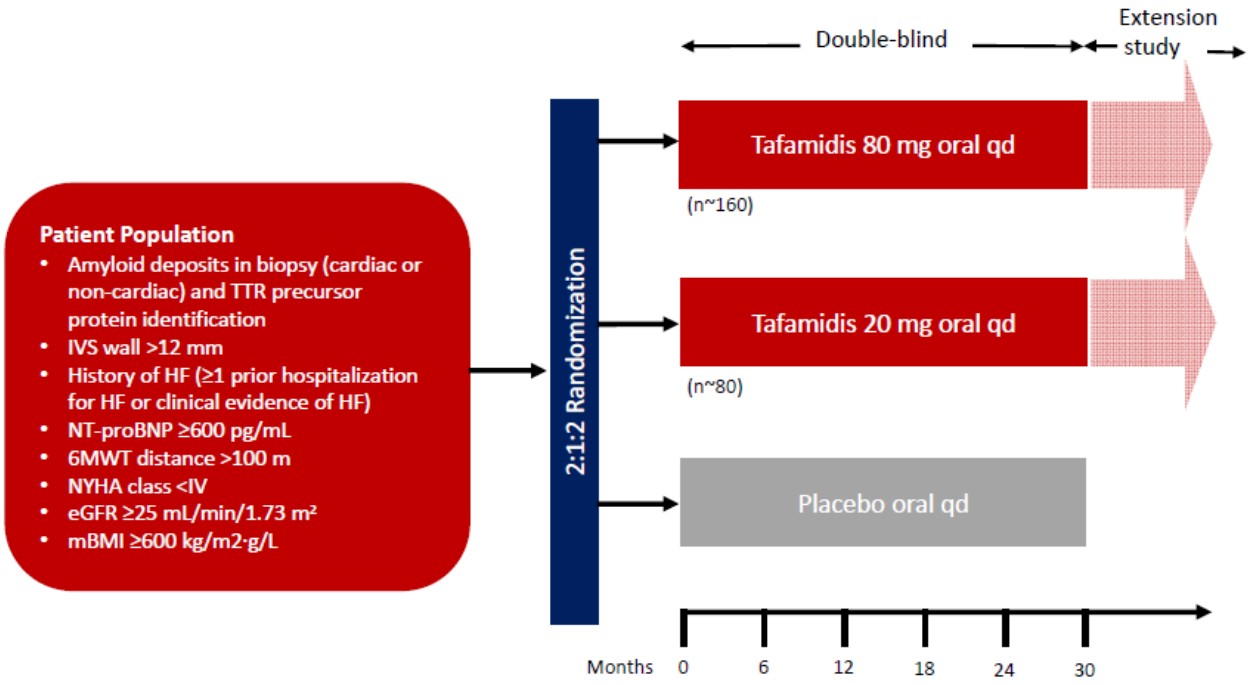
Overview and Objective

The objective of this study is to determine the efficacy, safety, and tolerability of daily oral dosing of tafamidis meglumine 20 mg or 80 mg compared to placebo in subjects with ATTR-CM. It is the single pivotal phase 3 trial supporting this application for the cardiomyopathy indication.

Trial Design

Study B3461028 was a 3-arm, parallel design with 2:1:2 randomization between the placebo, 20 mg tafamidis meglumine, and 80 mg tafamidis meglumine arms, respectively. Approximately 400 subjects were to be enrolled and followed for 30 months, at which time they had the option of rolling over into a blinded extension study (Study B3461045). The Schematic of Study B3461028 is as follows (Sponsor Graphic):

Figure 1 Study Design of Study B3461028



Reviewer's Comment: This superiority versus placebo study design comports exactly with what the Division discussed with the Sponsor during the design phase of the trial and was the basis for the SPA Agreement Letter that was initially issued to the sponsor. The critical design elements were placebo control and two tafamidis doses, both of which were tested versus placebo for efficacy outcomes. This was not add-on therapy, as there are no approved treatments for ATTR-CM.

- Trial locations: This trial was to be conducted at 60 sites in the following countries: Belgium, Brazil, Canada, Czech Republic, Spain, France, Greece, Italy, Japan, Netherlands, Sweden, Great Britain, United States.

  Reviewer's comment: The majority of the enrollment in this pivotal trial came from the US. Trial data from outside the US is relevant, because the diagnostic criteria were stringent (see next section), and potential confounding concomitant medications were exclusionary from both enrollment and continued participation in the double-trial trial.

- Control group: Placebo control was appropriate for this trial in that comparative effectiveness with other agents is not in question – there are no approved therapies for

ATTR-CM in the US (or in any other jurisdiction we are aware of).

- Diagnostic criteria: The diagnostic criteria for entry into this trial was unambiguous. Study candidates were required to have the following:

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

    - wtATTR-CM defined by genotype. Genotype-negative subjects were required to demonstrate the presence of amyloid deposits in a biopsy tissue, and TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry. In the case where immunohistochemistry (IHC) outcome was equivocal such as staining suggestive of lambda or kappa light chains, a diagnosis of ATTR amyloidosis must be confirmed using one of the following tests: (a) mass spectrometry (b) immunohistochemistry with electron microscopy or immunoelectron microscopy or immune-gold microscopy (c) scintigraphy with tracer e.g. 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC- PYP [Pyrophosphate] and also 99mTC-HMDP [hydroxymethylene diphosphonate].

- Key inclusion criteria: This trial enrolled subjects meeting the above diagnostic criteria who were between the ages of 18-90 years at the time of randomization who had been hospitalized of heart failure (HF) or required diuretic therapy for objective evidence of HF at least once in the past, but who had been clinically stable with no CV hospitalizations within 2 weeks prior to baseline. Eligible subject also had to have an NT-proBNP concentration greater than 600 pg/mL, and the ability to complete greater than 100 meters on the 6-Minute Walk Test (6MWT).

- Key exclusion criteria: Subjects were excluded from the trial who had uninterpretable echocardiograms for wall thickness at screening, were taking non-allowed medications within 30 days prior to baseline (e.g. diflunisal, tauroursodeoxycholate and doxycycline), had modified body mass indexes (mBMIs) below 600 $kg/m^2*g/L$, had previously taken tafamidis, required ongoing treatment with calcium channel blockers or digitalis, had primary (light chain) amyloidosis, were prior recipients heart and/or liver transplants or an implanted cardiac mechanical assist device (CMAD), had renal failure requiring dialysis and/or an estimated glomerular filtration rate (eGFR) of less than 25 mL/min./1.73 m^2, required self-catheterization for urinary retention, were New York Heart Association (NYHA) Classification IV at screening or at baseline, had a history of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular (AV) nodal or

sinoatrial (SA) nodal dysfunction for which a pacemaker was indicated but had not be placed, and subjects with heart failure that in the opinion of the investigator was on the basis of ischemic heart disease (e.g. prior myocardial infarction with documented history of cardiac enzymes and ECG changes), or uncorrected valvular disease that was not primarily due to transthyretin amyloid cardiomyopathy.

- Dose selection: Protocol B346128 employs a four-fold range of doses (20 mg and 80 mg daily) based on clinical pharmacology studies in healthy volunteers suggesting that near-maximal TTR stabilization would be achieved by exposures at the higher dose.

  TTR stabilization was measured by immunoturbidimetry following 2-day denaturation in 4.8M urea. Since denaturation requires the denaturation of the tetramer to the monomer, the abundance of the tetrameric form is a direct function of tetrameric stability. TTR stabilization was calculated in two steps. First, the fraction of initial (FOI) stabilized tetramer was determined as:

  FOI = TTR Tetramer (mg/dL) post-denaturation / TTR Tetramer (mg/dL) pre-denaturation

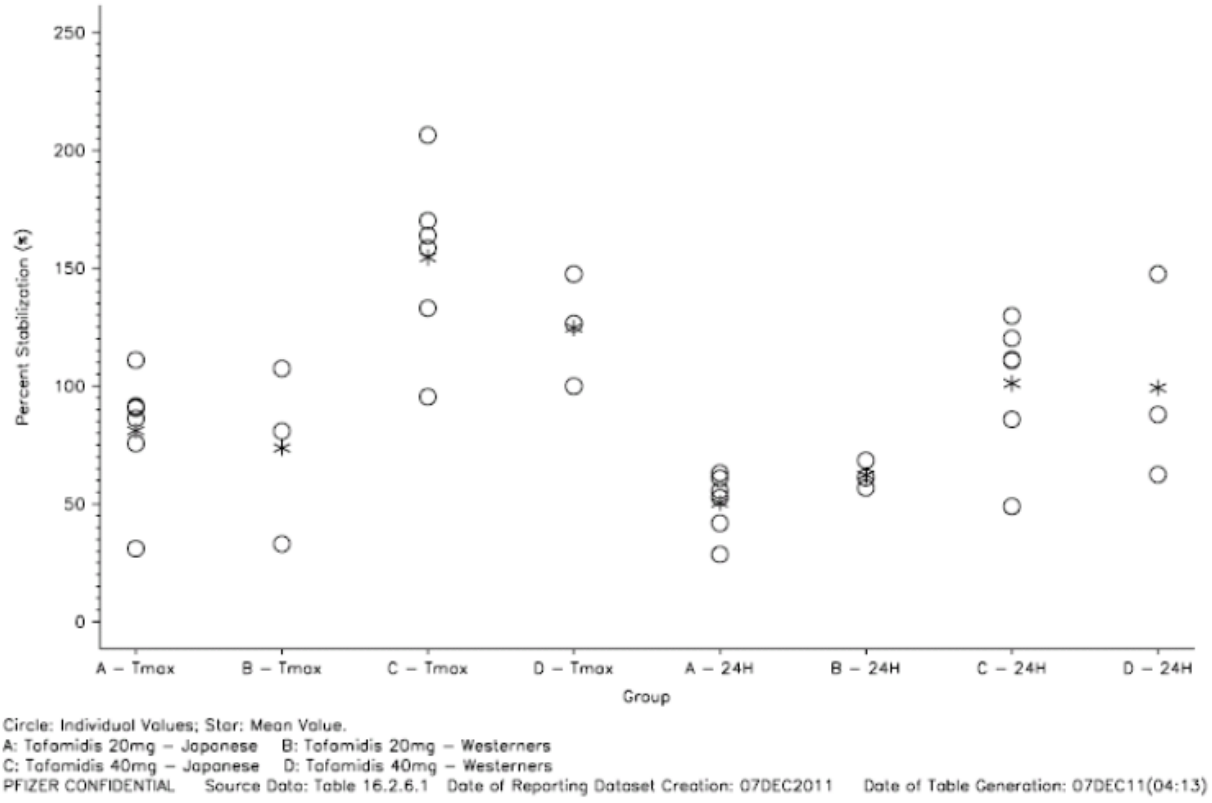
  Second, for each subject, the FOI was determined in duplicate before dosing with tafamidis meglumine ($FOI_{baseline}$) and at given time points after dosing with tafamidis meglumine (FOI_{dosed}). Percent stabilization of the tetramer was then calculated for these multiple post-dose timepoints as:

  Percent Stabilization = [(aveFOI Dosed – aveFOI Baseline) / aveFOI Baseline] x 100

  Note that using this method, 100% stabilization would represent a two-fold increase in FOI, whereas 200% stabilization would represent a three-fold increase in FOI.

  In clinical pharmacology study B3461009 in healthy normal subjects, tafamidis (maximum single dose 40 mg) demonstrated concentration dependent stabilization of the TTR tetramer per the figures below (sponsor final study report, pages 42-43):

Figure 2 Average Percent Stabilization of Transthyretin at Tmax and 24 hours Following Single Oral Doses of Tafamidis 20 mg and 40 mg in Japanese and Western Subjects



Circle: Individual Values; Star: Mean Value.
A: Tafamidis 20mg – Japanese B: Tafamidis 20mg – Westerners
C: Tafamidis 40mg – Japanese D: Tafamidis 40mg – Westerners
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.1 Date of Reporting Dataset Creation: 07DEC2011 Date of Table Generation: 07DEC11(04:13)

Source: Figure 16.2.6.2.3
T_{max} = time of maximum observed concentration.

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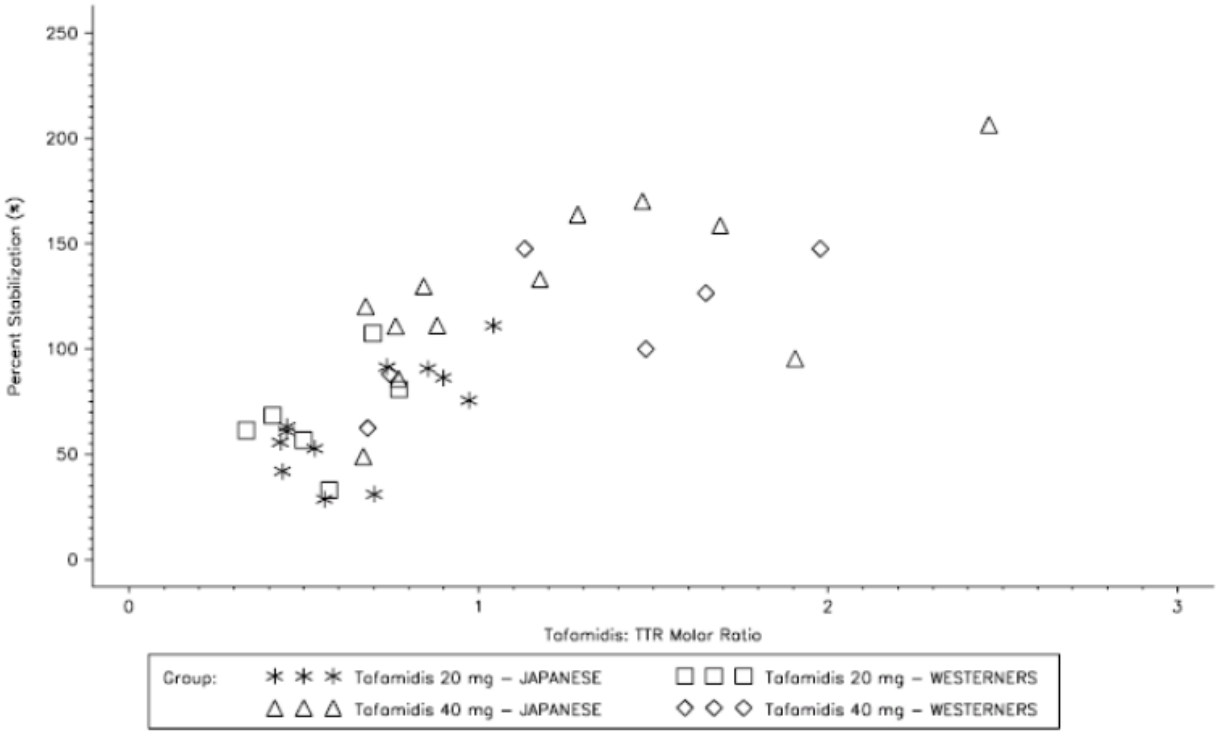
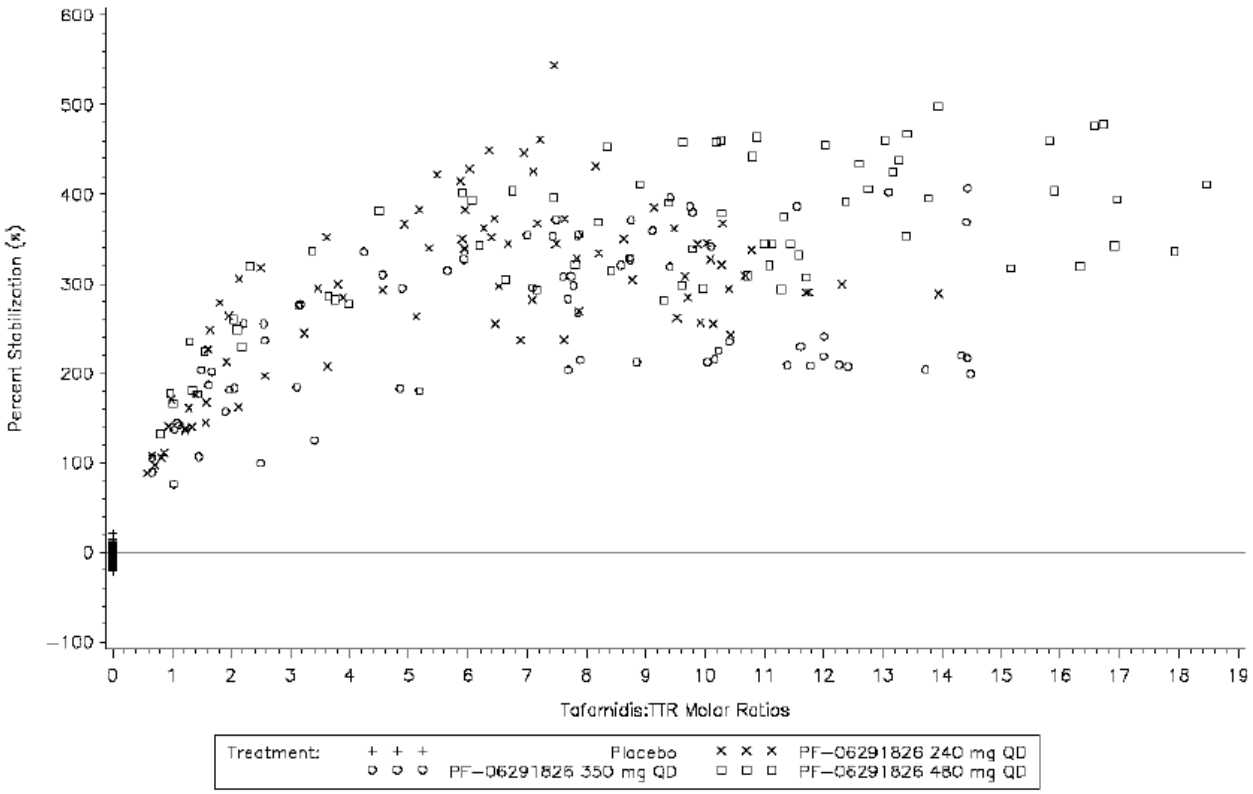
Figure 3 Percent Stabilization as a Function of Tafamidis: TTR Molar Ratio in All Samples (Linear Scale)



Source: Figure 16.2.6.2.1.1

At higher doses administered in clinical pharmacology study B3461040 (maximum single dose 480 mg), TTR percent stabilization increased with increasing tafamidis:TTR molar ratio and appeared to reach a plateau, per the figure below (sponsor final study report, page 41):

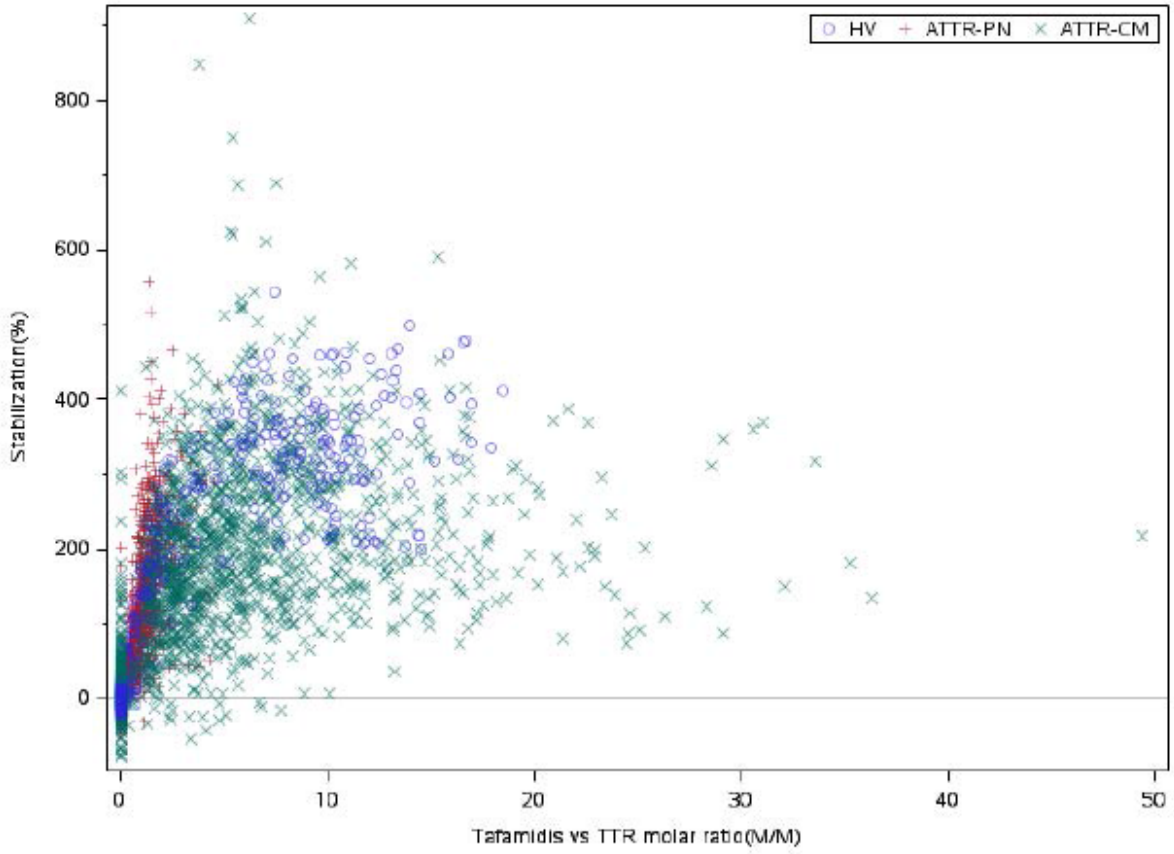
Figure 4 Scatter Plot of TTR Percent Stabilization vs Tafamidis:TTR Molar Ratio by Treatment (Linear Scale)



Source: Figure 14.4.7.2.1
Abbreviations: TTR= transthyretin; QD = once daily

The sponsor subsequently performed an exposure-response analysis evaluating the percent TTR stabilization versus the tafamidis:TTR ratio using all available human data (study PMAR-EQDD-B346b-Decision-Point-4-808-PKPD-Amendment). A total of 3662 stabilization observations from 102 healthy volunteers, 152 patients with ATTR-PN [20 Non-Val30Met], and 406 patients with ATTR-CM [340 wild type] were included. This analysis also demonstrated what appears to be a plateau in the TTR stabilization achieved with escalating tafamidis:TTR molar ratios, per the figure below (sponsor population PK study B345b-DP4-808 final report, page 35):

Figure 5 Relationship between TTRR and %TTR Stabilization



ePharmacology artifact ID RA15114611.
Abbreviation TTRR:tafamidis vs TTR molar ratio(M/M), HV:healthy volunteer, ATTR-PN:patient with transthyretin amyloid polyneuropathy, ATTR-CM:patient with transthyretin amyloid cardiomyopathy

In this study, subject status (healthy volunteers, patients with ATTR-PN and patients with ATTR-CM) were important predictors for both E_{max} and E_{50}. Healthy volunteers demonstrated the largest maximum stabilization (354%), followed by patients with ATTR-PN (279%), then patients with ATTR-CM (236%). A common E_{50} was estimated for patients with ATTR-CM and ATTR-PN (0.897). The E_{50} in healthy volunteers was estimated to be higher (2.23) compared to patients. Monte Carlo simulations from this population PK/PD model predicted that the mean percent TTR stabilization in patients with ATTR-CM at 6 months would be approximately 148% and approximately 205% following treatment with tafamidis meglumine 20 mg and 80 mg, respectively. The model indicated that the maximum drug effect (E_{max}) decreased over time, but the rate of decay was slow (-12.8%/year).

To confirm adequate exposures in the 80mg dose arm, the sponsor analyzed Month One pharmacokinetic (PK) samples at T_{max} from the first 50 subjects enrolled in the study to evaluate approximately 20 subjects assigned to the 80mg dose. The PK analyst was separate from the study team members and did not have access to the unblinded safety or efficacy data. The expected mean T_{max} concentration was 8.0 µg/mL. No adjustments were made to the 80mg dose arm on the basis of this analysis.

> *Reviewer's comment: The sponsor chose the 80 mg dose as the high dose to maintain adequate safety margins based on the non-clinical data (13x to 18x above the NOAEL in rats and 8.5x to 11x above the NOAEL in dogs based on the 61 mg free acid human AUC at steady-state), while achieving tafamidis:TTR molar ratios approaching or on the plateau region of TTR percent stabilization. This rationale was sound, and the dose range appropriate.*

- Assignment to treatment: Subjects were randomized in a 2:1:2 ratio to receive placebo, 20 mg tafamidis, or 80 mg tafamidis, respectively, in addition to standard of care therapy using an Interactive Response Technology (IRT) system to assign unique subject identification numbers sequentially to each subject who had signed in informed consent document (ICD). This number was retained through the duration of study participation. Subject eligibility for participation was determined following assessments during the Screening period and Baseline (Day 1) visit, with inclusion/exclusion criteria being evaluated per the judgement of the investigator. Treatment assignment was stratified by TTR genotype (variant or wild-type) and by baseline severity (NYHA Class I and NYHA Classes II combined, and NYHA Class III).

- Blinding: To maintain assigned dosing and proper blinding during the trial, clinical supplies were dispensed as blister packs of capsules to be taken daily. These blister packs contained either 3 capsules of blinded placebo and 1 capsule of blinded tafamidis 20 mg, 4 capsules of blinded tafamidis 20 mg, or 4 capsules of blinded placebo.

  > *Reviewer's comment: This reviewer requested and received blister packs of the clinical supplies from the Sponsor for inspection. There were two different capsule colors used during the trial (one off white and the other pale yellow). The off-white placebo tafamidis capsules were indistinguishable from the off-white tafamidis 20mg capsules. Likewise, the pale-yellow placebo tafamidis capsules were indistinguishable from the pale yellow tafamidis 20mg capsules. In that the placebo versus active tafamidis clinical supplies were indistinguishable, the adverse event experience with tafamidis was similar to placebo, and there were no demonstrable effects of tafamidis on vital signs, there is no reason to suspect the integrity of the blinding of the study.*

- Dose modifications/discontinuations: There were no protocol-driven dose escalations or dose reductions. Subjects who experienced AEs associated with poor tolerability to treatment with tafamidis that might impact dosing adherence had the option of blinded treatment re-assignment and potential dose reduction. In the event of a dose reduction, the dose consisted of 2 capsules of blinded tafamidis 20 mg and 2 capsules of matching blinded placebo. If poor tolerability continued following the blinded re-assignment, the site had the option to discontinue dosing for this subject and to terminate study participation. In the event of early study discontinuation, the site staff were to follow-up on the subject's vital/transplant status 30 months after randomization.

- Administrative structure: This was an international study conducted at 48 centers in 13 countries: Belgium (1), Brazil (1), Canada (1), Czech Republic (3), France (2), Germany (2), Italy (3), Japan (3), Netherlands (1), Spain (2), Sweden (2), United Kingdom (2), and United States (US) (25). The final protocol, amendments, and the ICD were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the study. The contract research organization (CRO) for the trial was (b) (4) Medical and clinical monitoring of the trial was performed by the sponsor and (b) (4) An independent Endpoint Adjudication Committee (EAC) determined the cause-specific nature of CV endpoints according to pre-defined endpoint criteria in the EAC charter. An external data monitoring committee (DMC) was managed by (b) (4)

- Schedule of procedures:

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Figure 6 Study Procedures and Scheduled in Study B3461028

Protocol Activity	Screening Period	Base Line		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)
Hematology	X	X	X	X		X		X		X		X		X
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (INR, PT – Local)[e]	X	X		X		X		X		X		X		X
Retinol Binding Protein		X		X		X		X		X		X		X
Serology (HBsAg, anti-HCV, and HIV)	X													
Serum/urine test for primary (light chain) amyloidosis (AL)	X													
Urinalysis	X	X		X		X		X		X		X		X
Genotyping	X													
Pregnancy test[f]	X	X		X		X		X		X		X		X
TTR stabilization, TTR oligomer concentration, and TTR concentration[g]		X		X		X		X		X		X		X
Urine TTR oligomer concentration[h]								X		X		X		X
Tafamidis Concentrations[i]		X		X		X		X		X		X		X
Tafamidis concentrations (for subjects receiving dialysis or hemofiltration)[j]			----------Any time during the study----------											
Diflunisal concentration[k]	X	X		X		X				X				X
Pharmacogenetic sample		X												
NT – proBNP, troponin I	X	X						X						X
6MWT	X	X				X		X		X		X		X
KCCQ[l]		X				X		X		X		X		X
EQ-5D-3L[m]		X				X		X		X		X		X
PGA[n]		X				X		X		X		X		X
NYHA classification[o]	X	X				X		X		X		X		X

Protocol Activity	Screening Period	Base Line		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)
Hematology	X	X	X	X		X		X		X		X		X
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (INR, PT – Local)[e]	X	X		X		X		X		X		X		X
Retinol Binding Protein		X		X		X		X		X		X		X
Serology (HBsAg, anti-HCV, and HIV)	X													
Serum/urine test for primary (light chain) amyloidosis (AL)	X													
Urinalysis	X	X		X		X		X		X		X		X
Genotyping	X													
Pregnancy test [f]	X	X		X		X		X		X		X		X
TTR stabilization, TTR oligomer concentration, and TTR concentration[g]		X		X		X		X		X		X		X
Urine TTR oligomer concentration[h]								X		X		X		X
Tafamidis Concentrations [i]		X		X		X		X		X		X		X
Tafamidis concentrations (for subjects receiving dialysis or hemofiltration)[j]			----------Any time during the study----------											
Diflunisal concentration[k]	X	X		X		X				X				X
Pharmacogenetic sample		X												
NT – proBNP, troponin I	X	X						X						X
6MWT	X	X				X		X		X		X		X
KCCQ [l]		X				X		X		X		X		X
EQ-5D-3L[m]		X				X		X		X		X		X
PGA[n]		X				X		X		X		X		X
NYHA classification[o]	X	X				X		X		X		X		X

Protocol Activity	Screening Period	Base Line		Month										
Concomitant medications[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record time of dosing				X		X		X		X		X		X
Record dosing adherence				X	X	X	X	X	X	X	X	X	X	X
Adverse Events reporting		X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Hospitalization determination		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense blinded medication		X			X	X	X	X	X	X	X	X	X	
Documentation of vital transplant and implant status[r]		X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Discussion[s]	X	X		X	X	X	X	X	X	X	X	X	X	

a. The Week 2 "visit" will allow the subject to either come to the clinic, or consist of a telephone call to the subject for specified data determination and having the subject go to a local laboratory or local physician's office to have their needed laboratory samples collected and shipped to the central laboratory.
b. Baseline (Day 1) ECG pre-dose.
c. Systolic and diastolic blood pressure and pulse rate (supine at least 3 minutes and standing at least 2 minutes prior to assessment), respiration rate and body temperature
d. Biopsy must be performed at Screening or have been performed and documented previously.
e. INR and PT will be determined at the site's local laboratory.
f. For women of childbearing potential. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
g. TTR stabilization, TTR oligomer concentration, and TTR concentration: Baseline (Day 1) sample: collect at any time pre-dose during the clinic visit. Month 1 sample: collect pre-dose and at 3 hours (± 1.5 hours) post-dose; Month 6 sample: collect at 7 hours (± 2.5 hours) post-dose; Month 12 sample: collect at 7 hours (± 2.5 hours) post-dose; Month 18 sample: collect at 1 hour (± 30 minutes) post-dose; Month 24 sample: collect at 1 hour (±30 minutes) post-dose; Month 30 sample: at any time during clinic visit.
h. Subjects at selected centers will provide a urine sample to be used in assay development for measurement of TTR oligomer concentrations in urine. For those subjects who provide consent, a 10 mL aliquot of urine will be collected (starting at the earliest possible prospective visit for the subject) at Months 12, 18, 24, and 30 (or Early Study Discontinuation); this aliquot will be obtained from the urine sample already collected for urinalysis at these visits.
i. Baseline (Day 1) tafamidis concentration sample: collect at any time pre-dose during the clinic visit. Month 1 tafamidis concentration sample: collect pre-dose and at 3 hours (±1.5 hours) post-dose; Month 6 tafamidis concentration sample: collect at 7 hours (± 2.5 hours) post-dose; Month 12 tafamidis concentration samples: collect at 7 hours (± 2.5 hours) post-dose; Month 18 tafamidis concentration sample: collect at 1 hour (± 30 minutes) post-dose; Month 24 tafamidis concentration sample: collect at 1 hour (± 30 minutes) post-dose; Month 30 tafamidis concentration: collect at any time during the clinic visit.
j. Should a subject require dialysis or hemofiltration at any time after randomization while on study treatment, the subject should have blood samples collected for tafamidis concentrations around the time of renal replacement therapy. The timing of the sample collection will depend on the type of renal replacement therapy administered. For hemodialysis or hemofiltration, samples should be collected on the date of the renal replacement therapy both prior to administration and after administration. When peritoneal dialysis is administered, the first sample should be collected at initiation of the first exchange. The second sample should be collected after the first exchange is completed (if performed outside of the home) or at least 24 hours after the initiation of the first exchange (if administered at home). Every effort should be made to collect these samples on the date of the subject's first administration of renal replacement therapy in the study; however, if this is not possible, the samples should be obtained as soon as possible on the date of a renal replacement therapy treatment. If necessary, the sample collection can be obtained using the guidelines for lab sample collection in the Guidance for Remotely Conducted Study Visits provided for the study. At the time of sample collection, the date and time of the last dose and the date and time of sample collection must be recorded.
k. Diflunisal concentration to determine if there is evidence of exposure to diflunisal prior to or during the study. Sample can be collected at any time during the clinic visit, after the ECG blood pressure and vital signs.
l. Kansas City Cardiomyopathy Questionnaire (KCCQ) (Appendix 1.1) should be completed before the EQ-5D-3L (Appendix 2) and PGA (Appendix 3).
m. EuroQoL-5 Dimensions (EQ-5D-3L) (Appendix 2) to be completed after the KCCQ (Appendix 1.1).
n. Patient Global Assessment (PGA) should be completed after the KCCQ (Appendix 1.1) and EQ-5D-3L (Appendix 2).
o. NYHA – New York Heart Association classification.
p. At the Screening visit, this will be Prior Medications.
q. Except for subjects who are randomized into the extension study (Study B3461045), all other subjects will have a 4-week (28 calendar days) safety follow-up visit after the last dose of the study medication for collection of adverse events. This visit can be completed by telephone.
r. When the Vital Status is determined, the subject should be asked if they have undergone a heart and/or liver transplant or implantation of cardiac mechanical assist device. This is especially important at the 30 month visit. If a subject indicates that they have had a transplant and they are still enrolled in the study, they should be removed from the study.
s. For all subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active; at each study visit, discuss with the subject the need to use highly effective contraception consistently and correctly, instruct the subject to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected and document such conversation in the patient chart.

- Dietary restrictions/instructions: None.

- Concurrent medications: Prior medications were those taken with 28 days prior to the first dosing of trial medication. Medications taken after first dose of trial medication were defined as concomitant medications. Medications indicated as standard of care other than diuretics were required to be stable for at least four weeks prior to Baseline. Changes in diuretic doses were permitted within 4 weeks of the Baseline visit. Some non-steroidal anti-inflammatory drugs (NSAIDs) can bind to the thyroxine (T4) binding sites on TTR, and so were prohibited medications that had to be stopped at least 30 days prior to Baseline. Specifically, diflunisal therapy had to be stopped 30 days prior baseline. Permitted NSAIDS

included: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac. The use of any other NSAIDS required agreement by the Sponsor's medical monitor. The uses of tauroursodeoxycholate and doxycycline were not permitted due to their possible interaction with amyloid fibrils. Digitalis and calcium channel blockers were also prohibited due to concerns that they bind to amyloid fibrils and could lead to increased toxicity from these drugs.

- Treatment compliance: Treatment compliance was determined by pill counts at each scheduled visit. Subjects were considered to be adherent to dosing requirements if they had taken four capsules of study medication per day on at least 80% of the days of study participation. Subjects with less than 80% dosing adherence were excluded from the per protocol analysis set.

- Rescue medications: None. There are no approved treatments for ATTR-CM except for supportive care with drugs like diuretics.

- Subject completion, discontinuation or withdrawal: All subjects were followed for the analysis of Month 30 study endpoint events whether or not they withdrew from study drug. While subjects were free to withdraw at any time, a signed Release of Medical Information Form (ROMI) was required for all subjects for the purpose of access to medical records as well as for obtaining vital status/transplant/cardiac mechanical assist device status follow-up with the subject's primary physician or with death registries. With Division concurrence, subjects who discontinued from the study due to transplantation or implantation of a cardiac mechanical assist device (CMAD) were handled in the primary analysis in the same manner as death. Withdrawal due to an adverse event (AE) will was distinguished from withdrawal due to other causes. "Censored" subjects were those who discontinued from the trial for reasons other than death.

Study Endpoints and Statistical Analysis Plan

As agreed to with the Division in the SPA for Study B3461028, the primary efficacy analysis employed a hierarchical combination of all-cause mortality and frequency of CV hospitalizations over the duration of the trial, comparing the placebo group to the pooled 20mg and 80mg tafamidis treatment group using the Finkelstein-Schoenfeld (FS) method.[5] There was no imputation of missing data for the primary efficacy analysis using the FS method. Using the FS method, each subject is compared to every other subject within each stratum in a pair-wise manner for trial outcomes and ranked. Mortality carries a higher importance in ranking that does CV hospitalization. Thus, the pairwise comparison proceeds in hierarchical

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

fashion using all-cause mortality first, assigning a +1 to the "better" subject and a -1 to the "worse" subject, as follows:

- If both subjects are dead, then the subject with a longer survival time is assigned +1, with the subject surviving the shorter time assigned -1
- If one subject is alive and the other is not, the live subject receives a +1 and the deceased one a -1
- If both subjects are alive, the comparison uses cardiovascular-related hospitalization to assign scores. The subject with the fewer cardiovascular-related hospitalizations (frequency) receives a +1 while the other receives -1
- The test statistic is based on the sum of these scores and stratified by TTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) resulting in a total of 4 strata (2 x 2).

To assess for the effect of missing data on the primary analysis, a two-stage imputation process was employed.[6] For this sensitivity analysis, the study duration of 30 months was to be partitioned into 3 periods of months 1-10, 10-20, and 20-30 (period 1, period 2, and period 3, respectively). Reduced exposure of dropouts during the intervals is represented by an exposure multiplier (between 0-10) of the monthly hospitalization rate.[7] Within each 10-month period, a Poisson regression model was used to derive a constant assumed rate for hospitalization counts as follows (no imputation of hospitalization for subjects who died):

- Period 1: estimated monthly hospitalization rate a function of the baseline covariates NHYA baseline classification and TTR genotype
- Period 2: estimated monthly hospitalization rate a function of the baseline covariates and the hospitalization counts during the first period
- Period 3: estimated monthly hospitalization rate a function of the baseline covariates and the hospitalization counts during the first and second periods.

Assuming success for the primary endpoint, the two key secondary endpoints would be evaluated as part of the p=0.05 alpha-conserving hierarchical analysis plan for controlling multiplicity in the following order:

1. Change from Baseline to Month 30 in distance walked during the 6MWT
2. Change from Baseline to Month 30 in Kansas City Cardiomyopathy Questionnaire KCCQ-Overall Summary score (KCCQ-OS).

[6] Rubin, D. (1987). Multiple Imputation for Non-response in Surveys, Wiley: New York.
[7] McCullagh, P., and Nelder, J. (1989). Generalized Linear Models, Second Edition, Chapman Hall/CRC: Boca Raton, FL.

These two key secondary endpoints were to be evaluated using a mixed model repeated measures analysis of covariance [ANCOVA (MMRM)] with an unstructured covariance matrix (or as appropriate); center and subject-within-center as random effects; treatment, visit, TTR genotype (variant and wildtype), and visit-by-treatment interaction, as fixed effects and baseline score as covariate, without imputation for missing data. Exploratory analyses of the key secondary endpoints included results from the MMRM analysis at each individual time point other than month 30. A supplementary/sensitivity pattern-mixture analysis was to be performed for the key secondary analyses to assess the robustness of their results on the basis of their dropout or missing-data patterns.

Other planned analyses included but were not limited to the components of the primary endpoint, assessing all-cause mortality using Kaplan-Meier (K-M) survival curves for each treatment group along with median survival times, as well as a Cox proportional hazards model with treatment, TTR genotype (variant and wild-type), and NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors. CV mortality was likewise to be assessed using these methods. Frequency of cardiovascular-related hospitalizations was to be analyzed using a Poisson regression analysis with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors adjusted for treatment duration. Key secondary and other endpoints were also to be evaluated for subgroups by TTR genotype (variant versus wild-type), NYHA Baseline classification, as well as dose (randomized dose group).

> *Reviewer's comment: This study was optimally designed to assess all three important outcomes: mortality, function, and quality of life.*

This statistical analysis plan was prospectively agreed to by the Division as part of the SPA process, as were its three subsequent amendments reflecting protocol changes that were agreed to by the Division as SPA modifications. For survival analyses, subjects who died for reasons other than cardiovascular (including "indeterminate") were to be designated as censored at the time of death. All subjects were to be followed for the analysis of Month 30 study endpoint events whether or not they withdrew from study drug. No interim efficacy analysis was planned.

The analysis sets were defined as follows:

- Randomized Set – all randomized subjects
- Safety Set – all randomized subjects who received at least 1 dose of study drug
- Intent-to-Treat (ITT) Set (primary analysis) – all subjects in the safety analysis set who had at least 1 post-baseline efficacy evaluation (i.e., post-baseline hospitalization, study

visit, or death)
- Per Protocol Set – all subjects in the ITT set who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis, to include a requirement for dosing adherence of at least 80% (those subjects who took 4 capsules of study medication per day on at least 80% of the days of study participation).

Treatment misallocations were to be treated as follows:

- Subjects randomized but not treated were to be excluded from the ITT and PP analysis sets for efficacy evaluations and excluded from the safety analyses
- Subject treated but not randomized were to be excluded from the efficacy analyses since randomized treatment would be missing, but would be reported under the treatment they actually received for all safety analyses
- Subjects randomized but taking the incorrect treatment were to be reported under their randomized treatment group for all efficacy analyses, but reported under the treatment they actually received for all safety analyses.

Protocol Amendments

The original protocol was dated 31 July 2013. The first-subject-first-visit occurred on 9 December 2013. The last-subject-last-visit occurred 7 February 2018. There were three protocol amendments during the course of the trial, each of which underwent clinical and statistical review that resulted in SPA Modification Agreement Letters being submitted to the sponsor. Those three amendments were as follows:

- Amendment 1 (dated 16 April 2014) – added tauroursodeoxycholate and doxycycline to the list of excluded medicines, and expanded the 30 month Vital Status determination to include transplant status
- Amendment 2 (dated 24 May 2016) – clarified that subjects implanted with a cardiac mechanical assist device would be withdrawn from the study and treated in the primary efficacy analysis similarly to subjects who received heart and/or liver transplants (i.e. counted as deaths)
- Amendment 3 (dated 24 May 2016) – clarified that subjects who did not enroll in the extension study would be followed for 28 days after last dose for collection of AEs and that those subjects that enrolled in the extension study were monitored within that study, discontinued enrollment of subjects with wild-type genotype in order to increase the numbers of subjects with variant genotype, updated the description of the external appearance of the study drug due to a manufacturing site change, and

redefined the baseline groupings for the NYHA functional classification that would be used for the efficacy analysis, grouping subjects with NYHA Class I and II together to be compared against NYHA Class III because of the low number of Class I subjects.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsors final study report attests that, "This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants."

Financial Disclosure

Financial disclosure forms were obtained for all but one investigator in pivotal study B3461028 (Priscilla Fernandes, site 1064) and for all investigators and sub-investigators in its open-label extension study B3461045. Documentation of attempts to contact Dr. Fernandes on five occasions was included.

In the blinded study B3461028, there were 242 investigators and sub-investigators, of which none were sponsor employees and none received compensation that would be valued based on the outcome of the study. None had a significant equity interest in the Sponsor (as defined by 21 CFR 54.2(b). There were 13 investigators/sub-investigators with disclosable financial interests, and one investigator also had a proprietary interest in the product. Significant payments to these 13 investigators exceeded the $24,999 threshold amount, with the overwhelming majority of these payments being for work performed in consulting, meeting attendance, and, in most cases, speaker's fees. Some received research grants from the Sponsor. The one investigator with a proprietary interest was (b) (4) The FS statistic after excluding the five subjects enrolled at this site is 3.46 with a p-value of 0.0005, confirming that this site did not influence the overall study result.

To assess for the potential that site-specific data may have driven the overall trial results, the six highest enrolling sites were sequentially excluded from the dataset, and then the primary efficacy FS test statistic recalculated without those individual sites. Note that this list of six highest enrolling sites also included the three highest risk sites as identified by the site selection tool for potential audits. As shown in the table below, excluding any one of these six sites did

not impair the statistically significant benefit demonstrated by the FS test statistic (FDA Biostatistics):

Table 3 Sensitivity Analysis for the Impact of Specific Sites on the Primary Efficacy Results

			All-cause mortality						CV hospitalization					
			Tafamidis			Placebo			Tafamidis		Placebo		FS test excluding center	
SITEID	COUNTRY	Total Pt	Death	N1	Rate (%)	Death	N0	Rate (%)	N1	Total hosp	N0	Total hosp	test stat	p-value
1016	DEU	47	0	20	0	7	27	26	10	17	15	22	2.92	0.004
1013	USA	40	5	26	19	5	14	36	12	17	8	17	3.37	0.0008
1011	USA	30	6	18	33	6	12	50	7	12	6	12	2.96	0.003
1043	USA	29	8	20	40	4	9	44	8	15	6	10	3.33	0.0009
1037	FRA	23	8	18	44	3	5	60	15	41	3	10	3.51	0.0004
1002	USA	21	6	18	33	1	3	33	11	21	2	8	3.31	0.0009

As a sensitivity analysis for site-influence, the same sequential deletion of the highest enrolling sites was performed using all-cause hospitalization in place of CV hospitalization. Statistical significance of the FS statistic was maintained in each case, as shown in the table below (FDA Biostatistics):

Table 4 Sensitivity Analysis for the Impact of Specific Sites on the Primary Efficacy Results- with all-cause hospitalization

			All-cause mortality						All-cause hospitalization					
			Tafamidis			Placebo			Tafamidis		Placebo		FS test excluding center	
SITEID	COUNTRY	Total Pt	Death	N1	%	Death	N0	%	N1	Total hosp	N0	Total hosp	Test stat	p-value
1016	DEU	47	0	20	0	7	27	26	17	41	20	57	2.14	0.03
1013	USA	40	5	26	19	5	14	36	19	33	12	29	2.55	0.01
1011	USA	30	6	18	33	6	12	50	11	23	9	26	2.3	0.02
1043	USA	29	8	20	40	4	9	44	12	34	8	16	2.58	0.01
1037	FRA	23	8	18	44	3	5	60	16	81	4	15	2.78	0.005
1002	USA	21	6	18	33	1	3	33	14	35	2	8	2.5	0.01

Reviewer's comment: there was no site that drove the results of study B3461028, which mitigates concerns that any of the 13 sites with potential conflicts of interest may have impacted the pivotal trial results in an important way. In addition, the safety profile of tafamidis was non-adverse and there were no pharmacodynamic effects of the drug that may have functionally unblinded the study (e.g. effects on heart rate as in the case of beta-blockers). Finally, the sponsor incorporated the following elements into a strategy for minimizing the potential for bias during the course of the study:

- *Study B3461028 was conducted according to International Council for Harmonization (ICH) Good Clinical Practices (GCP) and Pfizer standard operating procedures (SOPS) in place at the time*
- *The current FDA Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators were checked where applicable*
- *Independent expert opinion was sought for input into study design*
- *The study was conducted double-blind, randomized, at multiple sites globally*
- *The sites and facilities performing the safety and efficacy evaluations were determined to be acceptable based on appropriate certification or historical performance and/or qualifications and credentials*
- *Frequent monitoring of investigator study sites was performed as defined in the clinical monitoring plan*
- *The validity of the data collected during the study was confirmed by standard monitoring procedures as outlined in the clinical monitoring plan*
- *Selected individual sites were internally audited*
- *Subjects were randomly assigned to a treatment group via a central randomization system. Study medications were dispensed accordingly within the randomization system*
- *An independent Data Monitoring Committee (DMC) was established to monitor the conduct of the study and review data at pre-specified time points. The review was facilitated by an independent statistician*
- *Appropriate statistical methods were employed and pre-specified in an approved statistical analysis plan.*

Disposition of subjects

Table 5 Study B3461028: Disposition of subjects (ITT, Clinical Reviewer)

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Placebo		Tafamidis Meglumine 20MG		Tafamidis Meglumine 80MG	
			Subject Count	%	Subject Count	%	Subject Count	%
Protocol Milestone	Medical Release Form	Medical Form Released	177	100.0	88	100.0	176	100.0
		Medical Form Not Released	0	0.0	0	0.0	1	0.6
	Missing	Informed Consent Obtained	177	100.0	88	100.0	176	100.0
		Randomization	177	100.0	88	100.0	176	100.0
	Reconsent Non-Verbal	Reconsent Obtained	34	19.2	12	13.6	33	18.8
Disposition Event	Long Term Follow-Up	Alive	105	59.3	65	73.9	127	72.2
		Death	34	19.2	9	10.2	24	13.6
	Notice Of Death	Disease Under Study	49	27.7	17	19.3	28	15.9
		Other	20	11.3	5	5.7	17	9.7
		Unknown	3	1.7	1	1.1	4	2.3
	Subject Summary	Completed	85	48.0	60	68.2	113	64.2
		Death	38	21.5	14	15.9	25	14.2
		Withdrawal By Subject	37	20.9	8	9.1	17	9.7
		Adverse Event	11	6.2	5	5.7	12	6.8
		Organ Transplantation	4	2.3	1	1.1	3	1.7
		Other	1	0.6	0	0.0	2	1.1
		Cardiac Mechanical Assist Device Implantation	0	0.0	0	0.0	2	1.1
		Protocol Violation	1	0.6	0	0.0	1	0.6
		Lost To Follow-Up	0	0.0	0	0.0	1	0.6

The total number of subjects randomized to study B3461028 was 441, with 177, 88, and 176 subjects randomized to the placebo, tafamidis 20mg, and tafamidis 80mg arms, respectively. These same numbers of subjects were present in the intent-to-treat (ITT) analysis set and the safety analysis set. Vital status was known for all subjects at month 30. Only one subject was lost to follow-up. The sponsor reports that the most common reasons for screen failures were enrollment closure for wild-type subjects, NT-proBNP <600 pg/mL, subjects being clinically unstable, and eGFR <25 mL/min/1.73 m^2.

Of the 441 randomized subjects, the proportions of subjects completing the trial were 48%, 68%, and 64% in the placebo, tafamidis 20mg, and tafamidis 80mg arms, respectively. Conversely, the proportions of subjects who died during the study were 22%, 16%, and 14% in the placebo, tafamidis 20mg, and tafamidis 80mg arms, respectively. Long-term follow-up of subjects who withdrew from study drug also demonstrated a lower mortality rate among tafamidis-treated subjects, with 19%, 10%, and 14% of placebo, tafamidis 20mg, and tafamidis 80mg subjects dying in long-term follow-up, respectively. Death rates were lower for tafamidis-treated subjects from the ongoing trial and from the long-term follow-up cohorts regardless of genotype (data not shown). Withdrawal due to adverse events was similar across the treatment arms. Overall, the reasons for premature discontinuation were as follows:

- Placebo – 37 no longer willing to participate; 11 due to an AE; 5 organ transplants; 1 protocol violation

- Tafamidis 20 mg – 8 no longer willing to participate; 5 due to an AE; 1 organ transplant
- Tafamidis 80 mg – 17 no longer willing to participate; 12 due to an AE; 5 organ transplants; 2 CMAD implant; 1 Lost to follow up; 1 protocol violation.

A total of 6 subjects received a blinded dose reduction: 2 in the tafamidis 80 mg group and 4 in the placebo group.

Protocol Violations/Deviations for Studies B3461028 and B3461045

The most frequent protocol deviation fell into the investigational product (IP) category, and specifically, the subcategory of "subjects took less than protocol-specified total daily dose/number of capsules." The high percentage of deviations in this category emanated from the definition that triggered this deviation: "any missed or incomplete dose." Missed doses occurred in 70%, 86%, and 89% of subjects in the tafamidis 20mg, tafamidis 80mg, and placebo arms, respectively. However, overall compliance in the trial, as defined by subjects taking 4 capsules of study medication per day on at least 80% of the days of study participation, was equally high across the trial arms at 95%. 98% and 97% of subjects from the safety analysis set of subjects taking tafamidis 20 mg, tafamidis 80%, and placebo for whom compliance data was available, respectively (see compliance section below).

The deviation subcategory of "prohibited concomitant medications were administered to/taken by subject" occurred in 24%, 21%, and 17% percent of subjects taking tafamidis 20 mg, tafamidis 80 mg, and placebo, respectively. The majority of these cases involved patients taking NSAIDS, doxycycline, digitalis, and calcium channel blockers without sponsor approval. This relatively high concomitant medication deviation subcategory was noticed by the sponsor in 2016, resulting in an internal review at Pfizer of all subjects involved at that point. After determining that no serious adverse events (SAEs) had as a result of these prohibited medications, the Sponsor issued a Protocol Deviation Alert Letter to all sites.

The deviation subcategory of "The 6MWT was not administered properly" occurred in 16%, 14%, and 24% percent of subjects taking tafamidis 20 mg, tafamidis 80 mg, and placebo, respectively. Instances of errors were first noted by the Sponsor in February 2015 when it was noted that the screening and baseline test durations at site 1058 were not 6 minutes 0 seconds for 10 of the 11 subjects at that site. Instead, the test duration was 5 minutes 20 seconds to six minutes 30 seconds. The sponsor retrained that site and performed a study-wide CRF review that found no other instances of this problem. Subsequently, in December 2016, the sponsor determined on the basis of site monitoring that the 6MWT was not being performed in accordance with protocol requirements in that 7 sites (1016, 1026, 1027, 1082, 1084, 1086, and 1094) were using a measuring wheel or tape to determine the test distance with signs on hallway walls and floors or chairs and/or boxes to mark the test course, as opposed to using

cones for path markers as described in the protocol. The Sponsor instructed these sites to continue to carry out the 6MWT in the same way they had already been doing, in order to maintain consistency, and ensure no impact on longitudinal assessment of study data.

The deviation subcategory of "SAE was not reported in the required timeframe specified in the protocol" occurred in 17%, 20%, and 15% percent of subjects taking tafamidis 20 mg, tafamidis 80 mg, and placebo, respectively. The Sponsor noted late SAE reporting from a number of study sites (1001, 1002, 1005, 1007, 1011, 1013, 1014, 1016, 1018, 1019, 1026, 1027,1037, 1039, 1041, 1043, 1046, 1050, 1057, 1058, 1059, 1062, 1063, 1065, 1067, 1073, 1074, 1077, 1083, 1095, 1109, 1110). Most of these cases involved either lack of understanding of the importance of reporting SAEs or the reporting process for them. The sponsor re-trained the sites involved to assure back up reporting plans were in place for off hours. Site 1037 had a large number of late SAE reports, and so the sponsor imposed SAE tracking on this site and amended its contract to increase time and resources for SAE processing.

Of note, the occurrence rate of the deviation subcategory of "Patient reported outcome questionnaires were not completed" was relatively low at 9%, 5%, and 6% percent of subjects taking tafamidis 20 mg, tafamidis 80 mg, and placebo, respectively.

Subject Demographics

Table 6 Study B3461028: Demographic characteristics of the primary efficacy analysis

Subgroup	Tafamidis Meglumine 20MG (N = 88) n (%)	Tafamidis Meglumine 80MG (N = 176) n (%)	Pooled Tafamidis (N = 264) n (%)	Placebo (N = 177) n (%)
Sex				
Female	5 (5.7)	18 (10.2)	23 (8.7)	20 (11.3)
Male	83 (94.3)	158 (89.8)	241 (91.3)	157 (88.7)
Age				
Mean	73.25	75.18	74.54	74.05
Standard Deviation	7.07	7.24	7.23	6.69
Minimum	51	46	46	51
Median	73.5	76	75	74
Maximum	86	88	88	89
Age Group				
Under 65 (AGE < 65)	11 (12.5)	16 (9.1)	27 (10.2)	15 (8.5)
Over 65 (65 <= AGE)	77 (87.5)	160 (90.9)	237 (89.8)	162 (91.5)
Race				
Asian	2 (2.3)	11 (6.2)	13 (4.9)	5 (2.8)
Black or African American	11 (12.5)	26 (14.8)	37 (14.0)	26 (14.7)
Other	0 (0.0)	3 (1.7)	3 (1.1)	0 (0.0)
White	75 (85.2)	136 (77.3)	211 (79.9)	146 (82.5)
Ethnicity				
Hispanic or Latino	3 (3.4)	4 (2.3)	7 (2.7)	7 (4.0)
Missing	1 (1.1)	1 (0.6)	2 (0.8)	0 (0.0)
Not Hispanic or Latino	84 (95.5)	171 (97.2)	255 (96.6)	170 (96.0)
Region				
Asia	2 (2.3)	10 (5.7)	12 (4.5)	5 (2.8)
Canada	0 (0.0)	1 (0.6)	1 (0.4)	0 (0.0)
Europe	23 (26.1)	56 (31.8)	79 (29.9)	63 (35.6)
South America	0 (0.0)	1 (0.6)	1 (0.4)	1 (0.6)
United States	63 (71.6)	108 (61.4)	171 (64.8)	108 (61.0)

Reviewer's comment: the overwhelmingly male patient population was undoubtedly driven by the fact that approximately 75% of the enrolled subjects were wild-type genotypes (see the table below for other baseline characteristics). Baseline demographics were relatively well balanced between the placebo and pooled tafamidis groups for a study of this sample size.

Table 7 Study B3461028: Other baseline characteristics

Subgroup	Tafamidis Meglumine 20MG (N = 88) n (%)	Tafamidis Meglumine 80MG (N = 176) n (%)	Pooled Tafamidis (N = 264) n (%)	Placebo (N = 177) n (%)
NYHA Class				
Class I	8 (9.1)	16 (9.1)	24 (9.1)	13 (7.3)
Class II	57 (64.8)	105 (59.7)	162 (61.4)	101 (57.1)
Class III	23 (26.1)	55 (31.2)	78 (29.5)	63 (35.6)
NYHA Grouping				
Class I/II	65 (73.9)	121 (68.8)	186 (70.5)	114 (64.4)
Class III	23 (26.1)	55 (31.2)	78 (29.5)	63 (35.6)
Genotype				
Variant	21 (23.9)	42 (23.9)	63 (23.9)	43 (24.3)
Wild-Type	67 (76.1)	134 (76.1)	201 (76.1)	134 (75.7)
Stratification Grouping				
Class I/II, Variant	12 (13.6)	22 (12.5)	34 (12.9)	24 (13.6)
Class I/II, Wild-Type	53 (60.2)	99 (56.2)	152 (57.6)	90 (50.8)
Class III, Variant	9 (10.2)	20 (11.4)	29 (11.0)	19 (10.7)
Class III, Wild-Type	14 (15.9)	35 (19.9)	49 (18.6)	44 (24.9)

Reviewer's Comment: There were numerically more NYHA Class III subjects in the placebo treatment arm. This was confined to the Class III wild-type stratification grouping. Given that the Genotype allocations were almost perfectly balanced, this likely represents the fact that genotype was the first stratification variable, resulting in "forced randomization" relative to heart failure class. It is notable that regardless of heart failure class, both wild-type and variant genotypes demonstrated similar mortality benefits with tafamidis therapy. Class III subjects, regardless of genotype, demonstrated a non-significant lean toward benefit with tafamidis therapy, though the hospitalization rate of this group increased. This may have been the consequence of preventing deaths in the Class III subjects with the result of increasing hospitalizations in that stratum. (see subgroup analysis).

Treatment Compliance

Overall treatment compliance as measured by pill counts was high, per the following table, corrected for the erratum noted by the sponsor for study B3461028 final study report Table 7 (due to Subject (b) (6) incorrectly being attributed a compliance to -48% instead of 86%):

Table 8 Dosing Adherence (Safety Analysis Set)

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
n	84	167	251	168
Overall				
<80%	3 (3.6%)	3 (1.8%)	7 (2.8%)	5 (3.0%)
≥80%	81 (96.4%)	164 (98.2%)	244 (97.2%)	163 (97.0%)

Efficacy Results – Primary Endpoint

The primary Finkelstein-Schoenfeld (FS) efficacy analysis of study B3461028 on ITT analysis set demonstrates an FS test statistic of 3.44 favoring the pooled tafamidis therapy group in the ranked analysis with p=0.0006, per the table below (FDA Biostatistics). Significant benefit was demonstrated in both the reduction of all-cause mortality and CV hospitalization frequency composite components at Month 30.

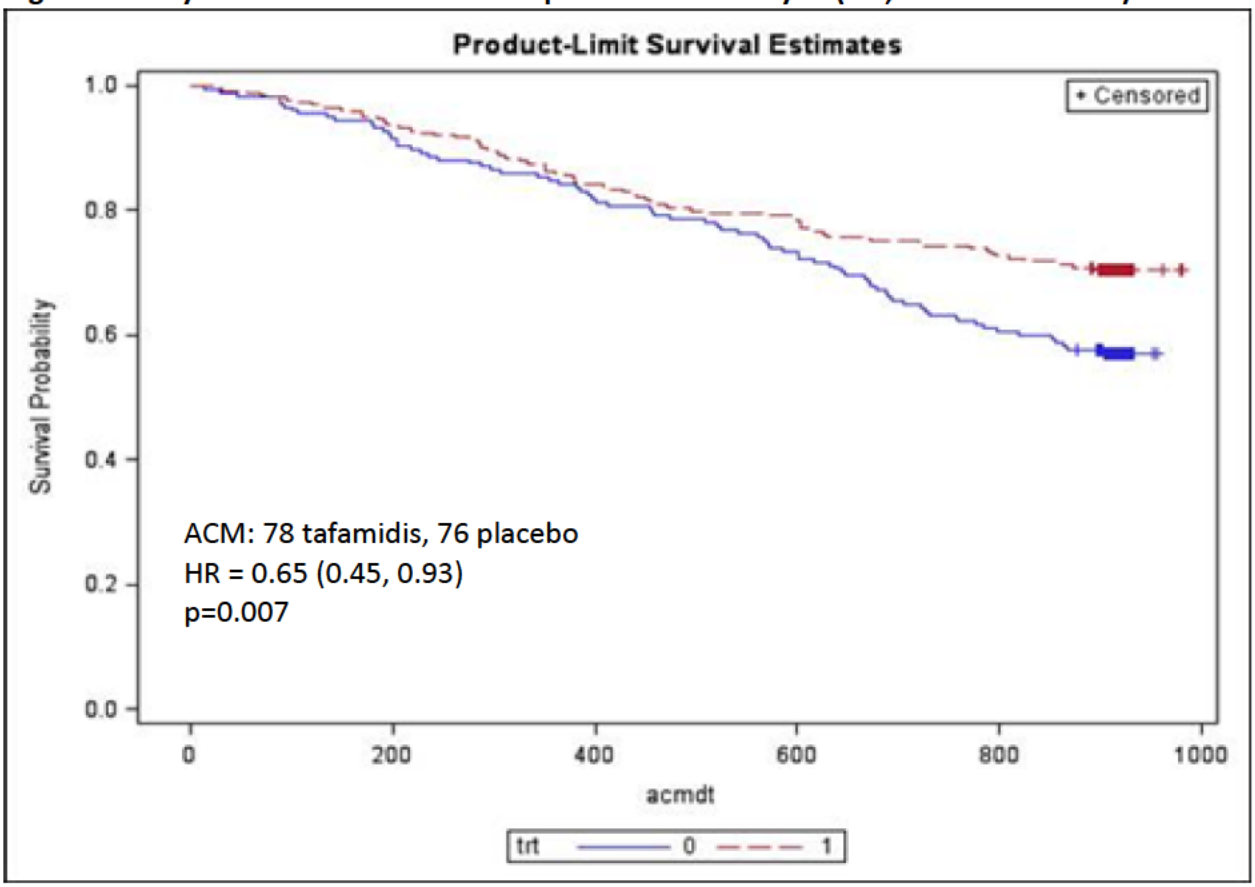
Table 9 Study B3461028: Primary Efficacy Endpoint (ITT Set) at Month 30 Finkelstein-Schoenfeld (FS) Analysis: All-Cause Mortality and Frequency of CV-Hospitalization (FDA Biostatistics)

	Pooled Tafamidis N=264	Placebo N=177	FS Test Statistic	P-value
Subjects alive n(%)	186 (70.5)	101 (57.1)		
Average CV hospitalizations during 30 months (per year) among those alive at Month 30	0.297	0.455		
All-cause death + CV Hospitalization			3.44	0.0006

The unadjusted Kaplan-Meier (K-M) for time to all-cause mortality (ACM) demonstrates a statistically significant benefit in favor of the pooled tafamidis treatment group [HR = 0.65 (0.45, 0.93)] with a visible separation of the mortality curves at approximately 500 days (16 months) of therapy, though the tafamidis treatment curve for ACM drops below that of the placebo ACM curve by approximately day 100, per the figure below (FDA biostatistics):

APPEARS THIS WAY ON ORIGINAL

Figure 7 Study B3461028: K-M ACM Component of FS Analysis (ITT, FDA Biostatistics)



Cause-specific K-M analysis of time to first non-CV death showed no significant difference between the pooled tafamidis group and the placebo arm, with benefit being confined to the reduction in CV death beginning at approximately day 450 of treatment, as shown in the two following K-M analysis of non-CV death and CV death, respectively:

APPEARS THIS WAY ON ORIGINAL

Figure 8 Study B3461028: K-M non-CV death (ITT, FDA Biostatistics)

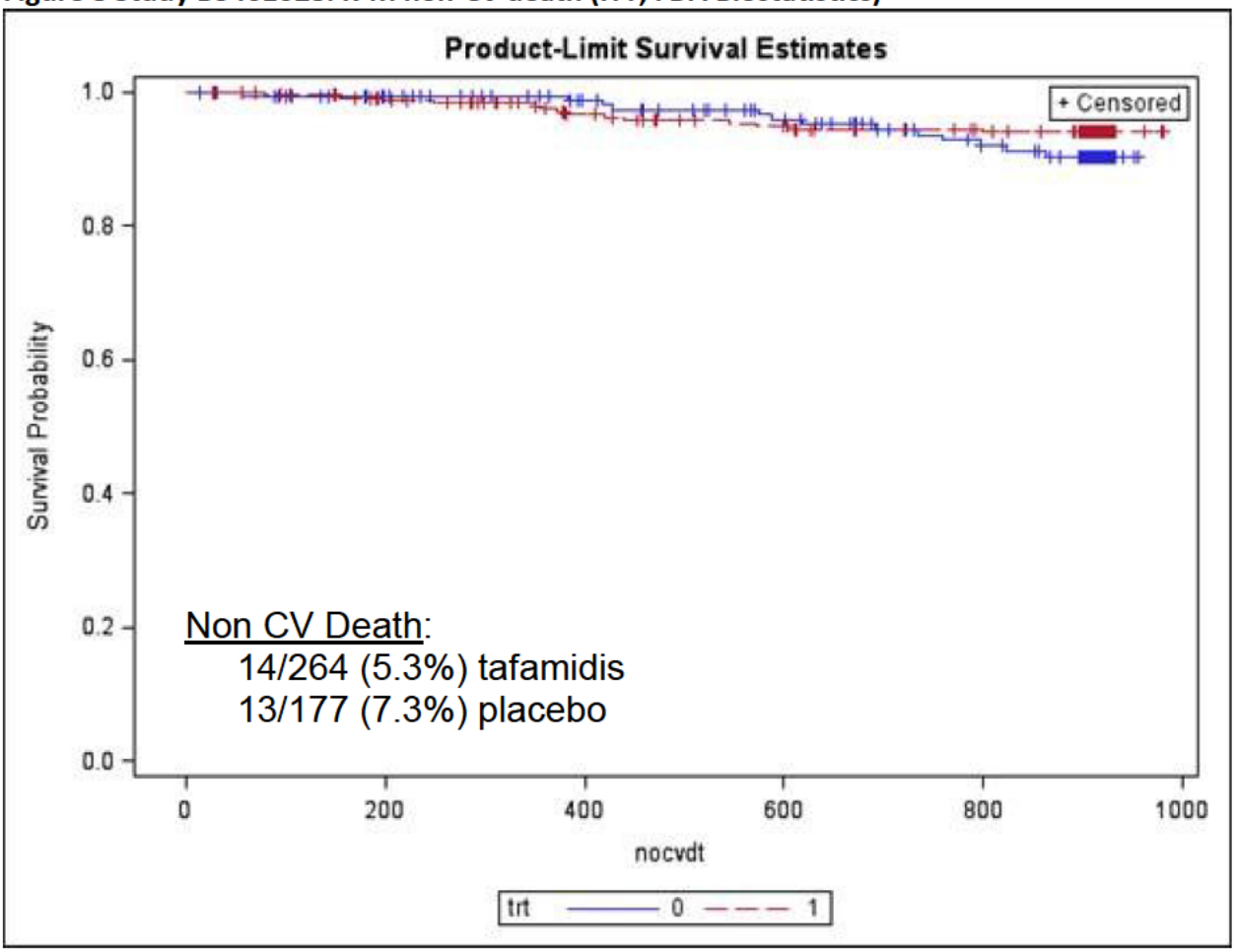
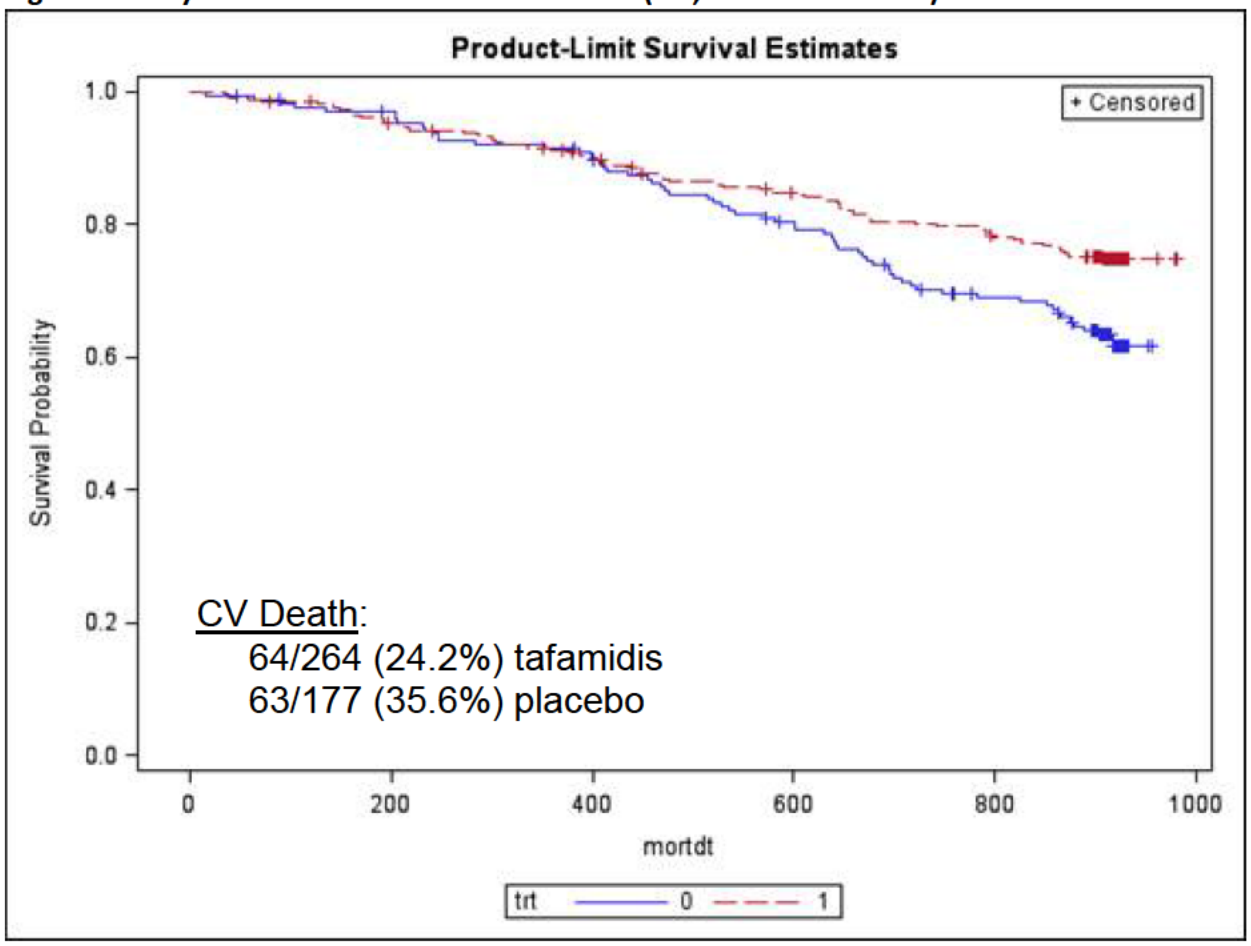


Figure 9 Study B3461028: K-M time to CV death (ITT, FDA Biostatistics)



Primary Efficacy Result by region, dose, genotype, and heart failure class

The Finkelstein-Schoenfeld analysis was subsequently applied to subgroups to look specifically at the treatment effect of tafamidis on the ranked composite endpoint by dose, region (US and non-US subjects, doses pooled), genotype (doses pooled), and NYHA class group (doses pooled). All subgroups demonstrated a statistically significant benefit, with the exception of variant and NYHA Class III subjects, who demonstrated a non-significant lean in the direction of benefit, per the table below (FDA Biostatistics):

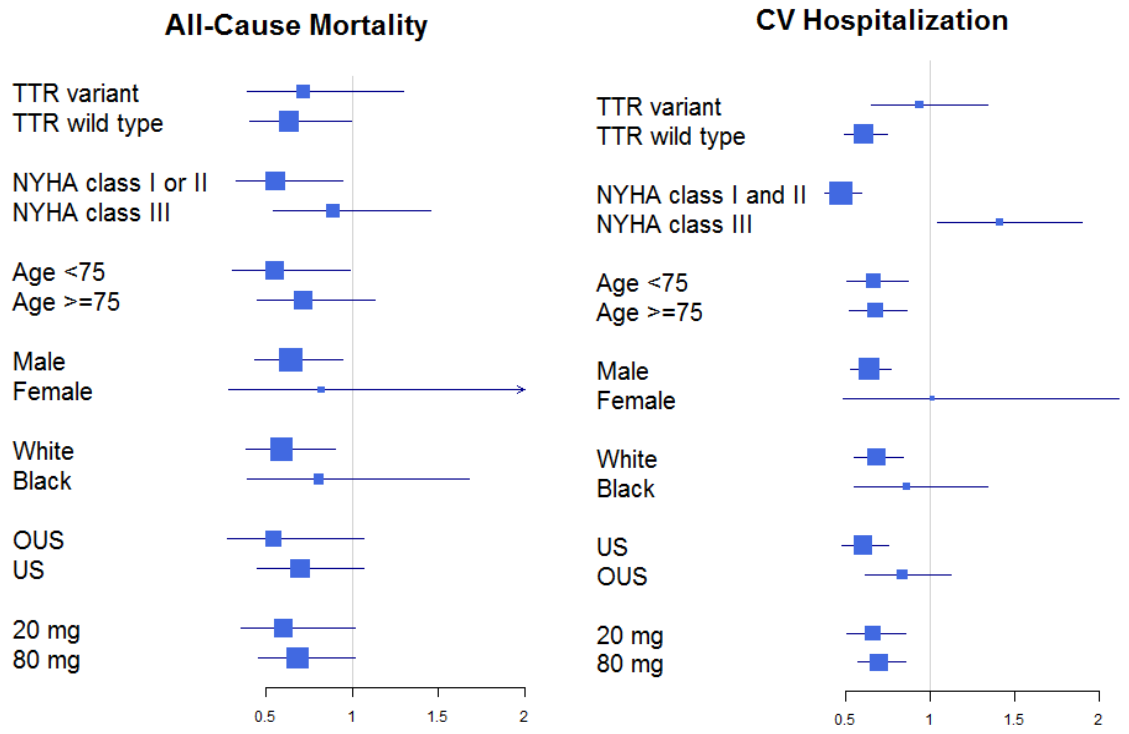
Table 10 Study B3461028: Month 30 FS result by region, dose, genotype, and NYHA stratification group

	N	Test Statistic	P-value
Overall population	441	3.44	0.0006
US (doses pooled) Non-US (doses pooled)	279 162	2.54 2.28	
20 mg versus placebo 80 mg versus placebo	265 353	2.82 2.97	
WT Variant	335 106	3.32 1.04	
NYHA Classes I & II NYHA Class III	300 141	3.48 0.3	

Subgroups Analyses for Components of Primary Efficacy Composite (ITT, FDA Biostatistics)

The components of the FS primary composite, ACM and CV Hospitalizations at month 30, were subsequently analyzed separately by the Hazard Ratio and Risk Ratio, respectively, per the forest plots below (Cox model for all-cause mortality, Poisson regression model for CV hospitalization, FDA biostatistics). All subgroups demonstrated a consistent beneficial effect of the point estimate for tafamidis therapy with respect to ACM. NYHA Class III subjects also demonstrated a lean toward ACM reduction though with an increase in CV hospitalizations, which would not be unexpected in the most seriously ill patient group (i.e. deaths averted at the cost of increased CV hospitalizations).

Figure 10 Study B3461028: Subgroup Analysis for Components of Primary Efficacy Composite



Data Quality and Integrity

Data quality was satisfactory for statistical review. An early question arose regarding methodology the sponsor used for deriving the rank score for the primary FS analysis. This issue was promptly answered by the sponsor such that no further issues in the efficacy review arose. No imputation was done for missing cases for the primary analysis based on the Finkelstein-Schoenfeld method. A signature of a release of medical information (ROMI) was a condition for entry into study B3461028 which gave the Sponsor permission to follow up vital status at month 30 to include transplant and cardiac assist device implant status (the latter two of which were treated as deaths in the agreed-to SPA analytical plan). Therefore, vital status was known for all subjects at the end of the study and this information was used for the primary efficacy analysis. For subsequent MMRM analyses on the 6MWT and KCCQ data, no imputation was performed.

Efficacy Results – Secondary and other relevant endpoints

Six-minute walk test (6MWT)

There were two key secondary endpoints in the hierarchical alpha-sparing analytical plan. The first was the least-squares mean change from baseline (BL) for the 6MWT at month 30, which demonstrated a statistically significant increase for the ITT population of 75.7 meters in the pooled tafamidis group relative to the placebo arm, as shown in the table below: (ITT, FDA Biometrics):

Table 11 Study B3461028: 6MWT Change from BL, in meters, at month 30 (ITT, FDA)

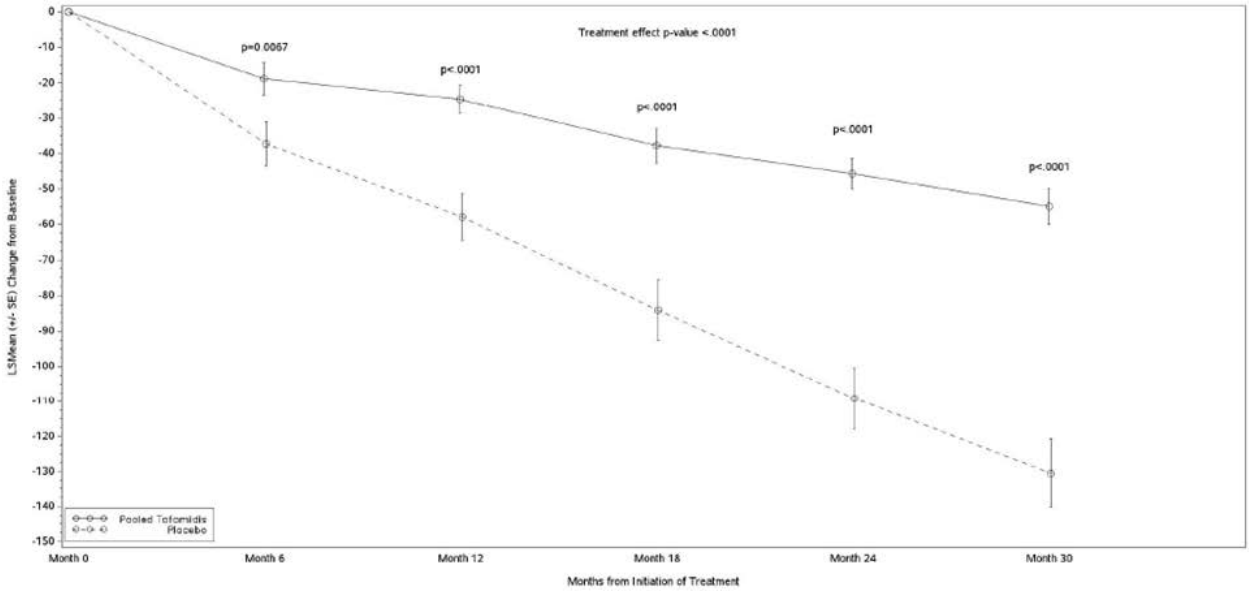
	Tafamidis pooled			Placebo				
	N	Mean	STD	N	Mean	STD	LS means	95% CI
Overall	155	-30.6	87.9	70	-89.7	105.1	75.7	(57.6, 93.8)
NYHA class I or II	132	-27.1	86.3	57	-93.5	110	85.4	(64.1, 106.7)
NYHA class III	23	-50	96.1	13	-72.9	82.1	31.6	(-11.7, 74.8)
TTR wild type	131	-24.4	89.5	62	-89.1	107.2	77.1	(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)

As can be seen from the table above, the benefit of tafamidis theray was nominally significant regardless of genotype or dose. The NYHA Class I or II stratification group demonstrated the greatest increase (85.4 meters). NYHA Class III patients demonstrated a 31.6 meter lean toward benefit, but that confidence interval crossed zero.

Reviewer's comment: The fact that there were more dropouts in the placbo arm of study confers reassurrance that there is no survivor's effect contributing to the 6MWT result at month 30.

The sponsor also performed an ANCOVA-MMRM anlaysis of 6MWT results that were performed every six months throughout the study. The sponosr anlaysis, which was confirmed by FDA, demonstrated a nominally significant benefit at month 6. The magnitude of the benefit progressively increased with each successive 6MWT as shown in the figure below:

Figure 11 Study B3461028: 6MWD LS Means (SE) Change From BL to Month 30 – Pooled Active Treatment (ITT Analysis Set, Sponsor)



FDA then reanalyzed the MMRM of the 6MWT by dose, demonstrating that the 20mg and 80mg doses conferred essentially identical benefits over the course of the study, as shown in the figure below:

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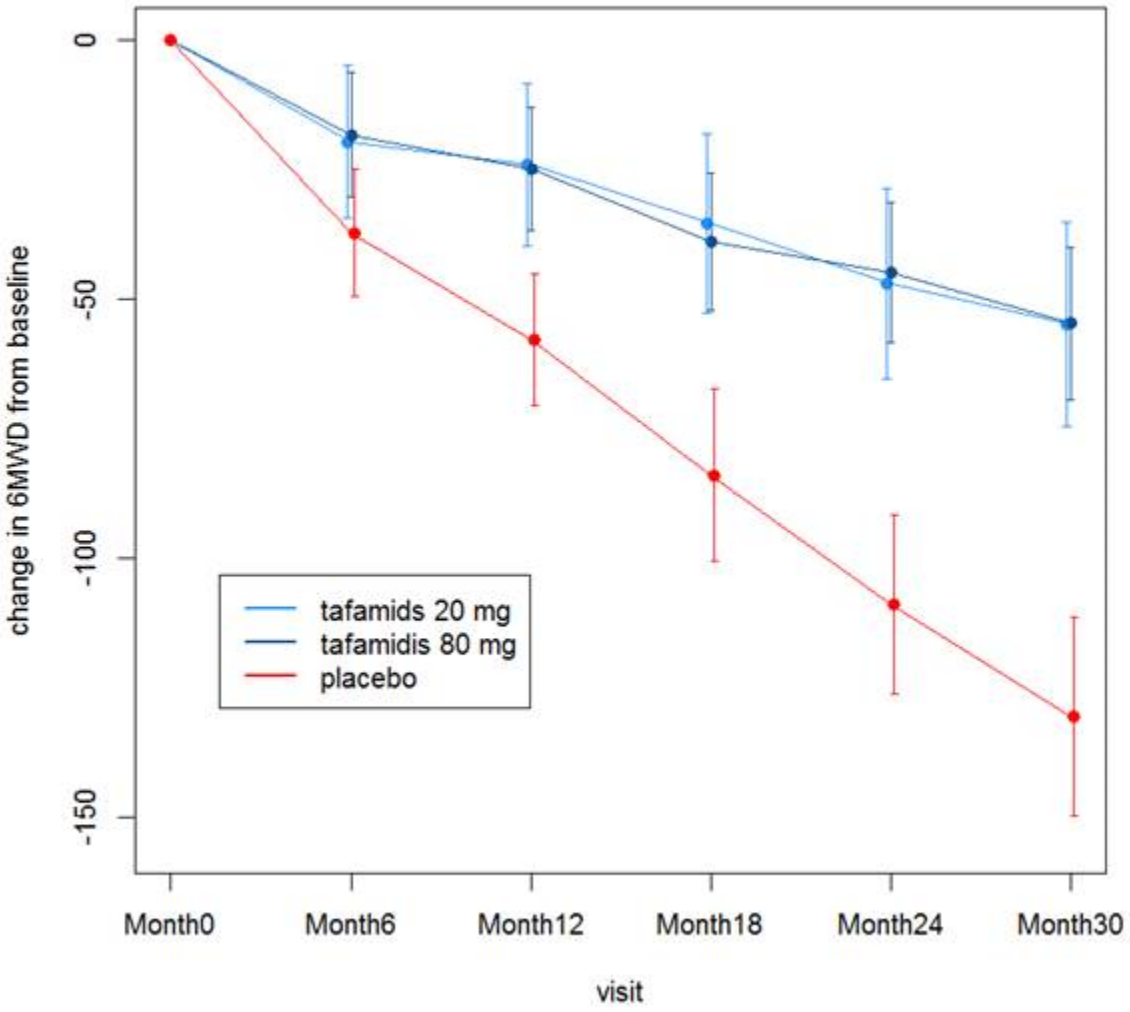
Figure 12 Study B3461028: 6MWD LS Means (SE) Change from BL to Month 30 by Dose (ITT set, FDA)



Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OS)

The second key secondary endpoint in the hierarchical alpha-sparing analytical plan was the month 30 change from baseline in the KCCQ-OS, which demonstrated a statistically significant

increase in the ITT population of 13.7 points in the pooled tafamidis group relative to the placebo arm, as shown in the table below: (ITT, FDA Biometrics):

Table 12 Study B3461028: KCCQ-OS Change from BL at month 30 (ITT, FDA Biometrics)

	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)

As can be seen from the table above, nominally significant improvement was seen regardless of genotype, dose, or NYHA stratification group.

> *Reviewer's comment: It is once again reassuring that there were more premature dropouts in the placebo arm, suggesting that there is no survivor's effect in this result. I note that although the KCCQ-OS had been the agreed-to metric for this patient reported outcome result during the SPA process, the Clinical Outcomes Assessment (COA) reviewer that attending our pre-NDA meeting with the sponsor expressed a concern that the KCCQ-OS includes domains (e.g., self-efficacy, quality of life, and social limitation) that are affected by various factors that may not be directly related to treatment and therefore is difficult to interpret. That reviewer expressed COA's current thinking that the KCCQ Total Symptom Score (KCCQ-TS) and KCCQ Physical Limitation Score (KCCQ-PL) are more meaningful and interpretable to support labeling, and recommended that the sponsor also submit the results of these two KCCQ scores with the NDA. Accordingly, the sponsor submitted a comprehensive breakdown of KCCQ score results to support labeling demonstrating the nominal significance of their KCCQ-TS and KCCQ-PL results as well, per the following sponsor table which have been verified by FDA Biometrics:*

Table 13 Study B3461028: KCCQ-OS Change from BL by subcomponent at month 30

Endpoints	***Baseline Mean (SD)***		***Change from Baseline to Month 30, LS Mean (SE)***		***Treatment Difference from Placebo LS Mean (95% CI)***
	Pooled Tafamidis N=264	***Placebo N=177***	***Pooled Tafamidis***	***Placebo***	
6MWT (meters)	*350.55 (121.30)*	*353.26 (125.98)*	*-54.87 (5.07)*	*-130.55 (9.80)*	*75.68 (57.56, 93.80)*
KCCQ-OS	*67.27 (21.36)*	*65.90 (21.74)*	*-7.16 (1.42)*	*-20.81 (1.97)*	*13.65 (9.48, 17.83)*
KCCQ-TS	*73.45 (20.27)*	*72.11 (20.64)*	*-6.26 (1.36)*	*-18.75 (2.31)*	*12.48 (8.13, 16.84)*
KCCQ-SF	*73.42 (21.85)*	*70.90 (22.49)*	*-6.53 (1.44)*	*-19.37 (2.66)*	*12.85 (7.30, 18.39)*
KCCQ-SB	*73.58 (20.72)*	*73.31 (20.82)*	*-6.04 (1.50)*	*-17.91 (2.341)*	*11.87 (7.75, 16.00)*
KCCQ-PL	*69.07 (22.77)*	*68.24 (24.18)*	*-9.98 (1.33)*	*-22.62 (2.21)*	*12.64 (8.54, 16.75)*
KCCQ-QL	*62.63 (24.73)*	*59.98 (24.65)*	*-1.53 (1.83)*	*-15.94 (2.38)*	*14.40 (9.07, 19.74)*
KCCQ-SL	*63.36 (28.96)*	*63.10 (28.97)*	*-8.79 (2.09)*	*-24.66 (2.92)*	*15.87 (10.34, 21.40)*

The sponsor also performed an ANCOVA-MMRM analysis of KCCQ-OS results that were performed every six months throughout the study. The sponsor analysis, which was confirmed by FDA, demonstrated a nominally significant benefit at month 6. The magnitude the benefit progressively increased with each successive KCCQ-OS as shown in the figure below:

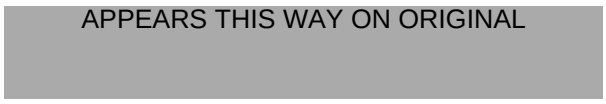
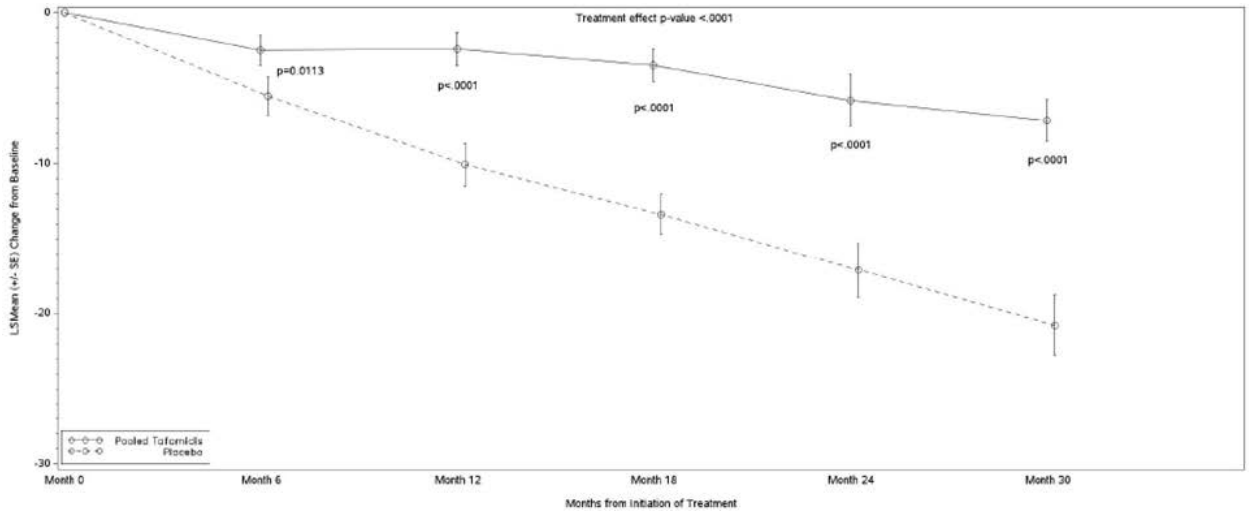


Figure 13 Study B3461028: KCCQ-OS Change from BL at month 30 KCCQ-OS LS means (SE) change from baseline to month 30 – Pooled Active Treatment (ITT Analysis Set, Sponsor)



FDA then reanalyzed the MMRM of the KCCQ-OS by dose, demonstrating that the 20mg and 80mg doses conferred essentially identical benefits over the course of the study, as shown in the figure below:

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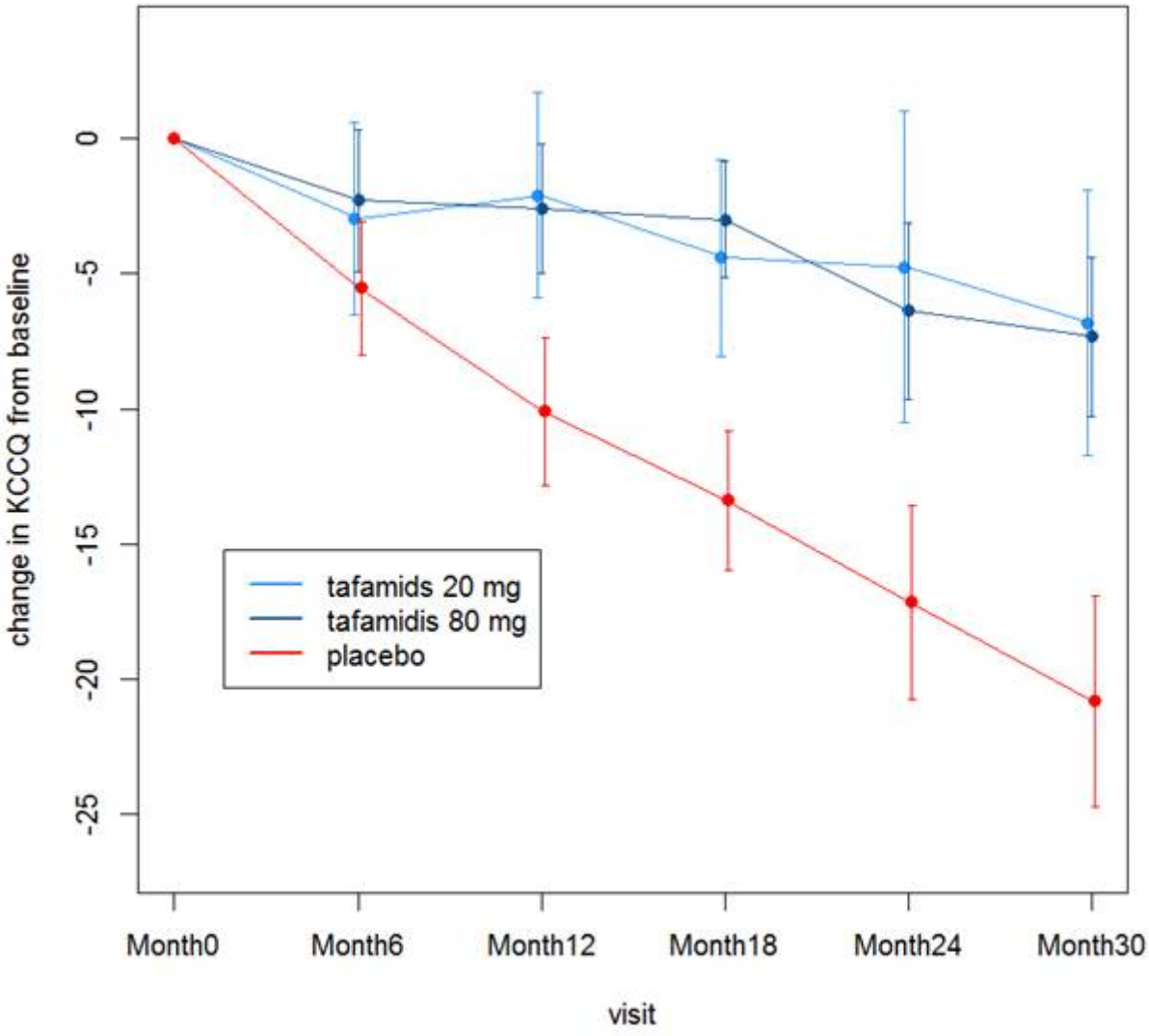
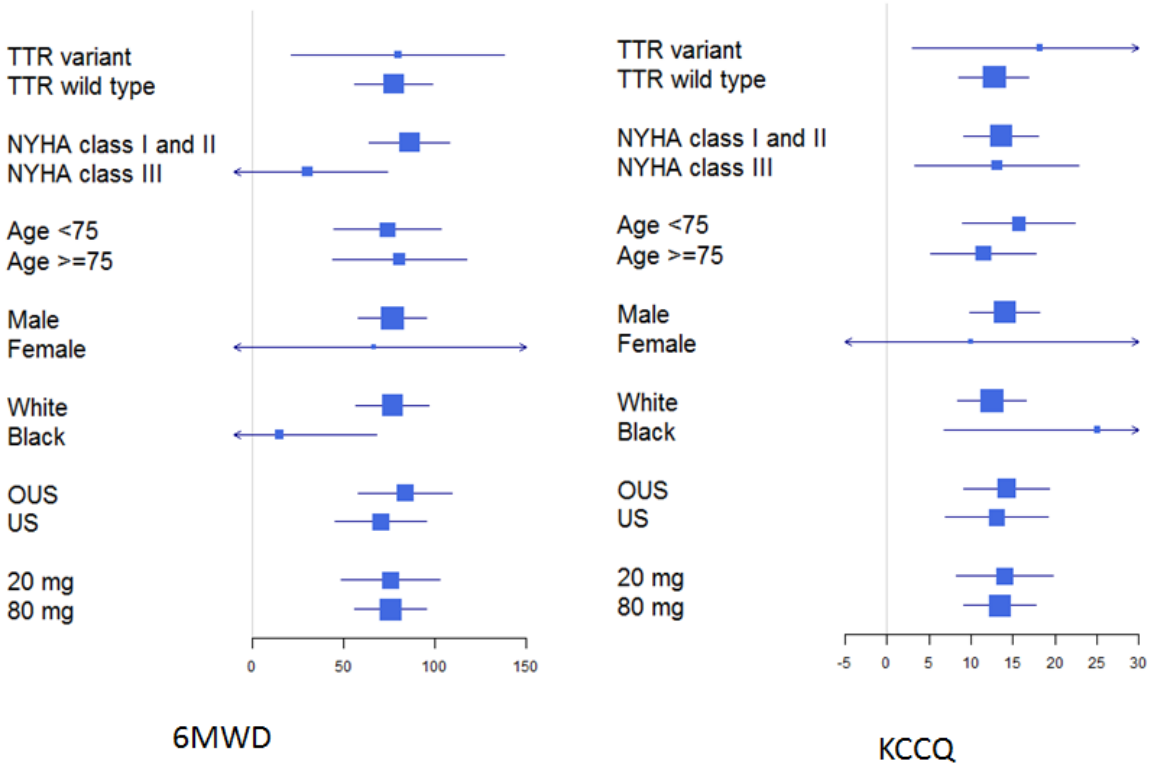
Figure 14 KCCQ-OS LS Means (SE) Change from Baseline to Month 30 by Dose (ITT Set, FDA)



Subgroups Analyses for 6MWT and KCCQ

The components of the 6MWT and KCCQ-OS key secondary endpoints at month 30 were subsequently analyzed respectively per the forest plots below (MMRM). All subgroups demonstrated a consistent beneficial effect of tafamidis therapy with respect to both the 6MWT and the KCCQ-OS.

Figure 15 Study B3461028: Subgroup Analysis for 6MWT and KCCQ



Durability of Response

Kaplan-Meier curves for ACM, 6MWT, and KCCQ continue to diverge in favor of the tafamidis treatment group out to month 30.

Persistence of Effect

Not applicable: there were no protocol-driven periods of discontinuation in study B3461028.

Additional Analyses Conducted on the Individual Trial

Alternative Components of the Primary Efficacy Composite

FDA modified the primary endpoint to encompass either CV death and CV hospitalization, or ACM and all-cause hospitalization. Per the figure below, the FS analysis maintained statistical significance whether cause-specific components were used in the composite or not:

Table 14 Month 30 Finkelstein-Schoenfeld Analysis Subgroups by Cause of Death or Hospitalization Pooled Tafamidis versus Placebo (FDA)

	Test Statistic	P-value
CV death + CV hospitalization	3.89	<0.001
all-cause death + all cause hospitalization	2.62	0.009

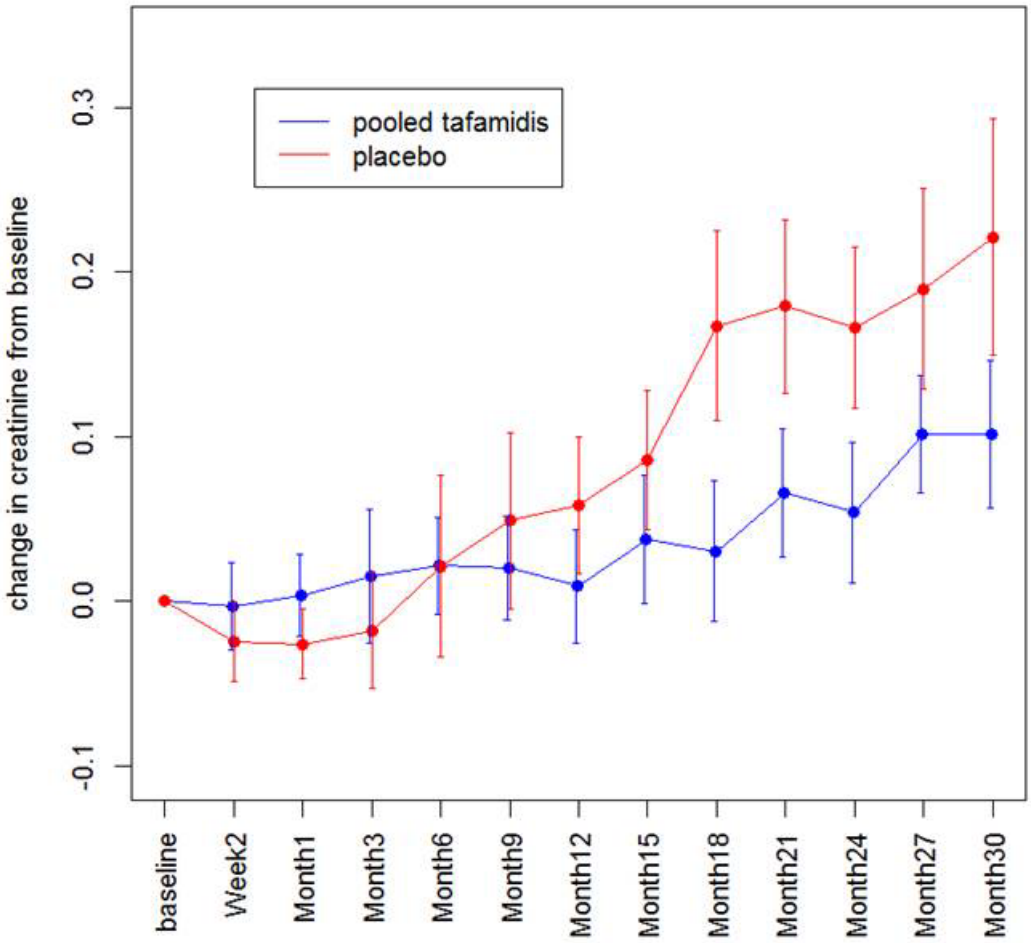
Renal Function Changes to Month 30

The slowing of renal function deterioration at Month 30 compared to baseline was assessed by least square mean difference between baseline and the pooled tafamidis treatment group at each time point where creatine was assessed at scheduled visits. The curves for the placebo and the pooled tafamidis group began to separate in favor a tafamidis therapy at month 6 and became nominally significant at Month 18, with p-values that remained essentially zero from months 18 to 30 as the curves appear to continue to separate. The renal function data table and its accompanying figure are shown below (FDA Biostatistics):

Table 15 Study B3461028: Change from baseline in creatinine by visit

Visit	LS Mean Difference	SE	nominal p-value	95% CI Lower	95% CI Upper
Week 2	-0.0214	0.016	0.170	-0.052	0.009
Month 1	-0.0293	0.013	0.029	-0.056	-0.003
Month 3	-0.0330	0.022	0.128	-0.075	0.009
Month 6	-0.0001	0.028	0.997	-0.055	0.055
Month 9	0.0292	0.032	0.367	-0.034	0.093
Month 12	0.0488	0.030	0.101	-0.009	0.107
Month 15	0.0479	0.029	0.101	-0.009	0.105
Month 18	0.1372	0.031	<.0001	0.077	0.197
Month 21	0.1137	0.031	0.000	0.052	0.175
Month 24	0.1122	0.032	0.001	0.049	0.176
Month 27	0.0883	0.032	0.005	0.026	0.150
Month 30	0.1201	0.040	0.003	0.042	0.199

Figure 16 Study B3461028: Change from baseline in creatinine by visit



7. Integrated Review of Effectiveness

The single, multicenter, international, randomized, placebo-controlled, Phase 3 study B3461028 that was conducted under an SPA with the Review Division was the principle source of data supporting the efficacy of tafamidis for ATTR-CM. (b) (4) There were no integrated efficacy datasets submitted with this application.

8. Review of Safety

8.1. Safety Review Approach

Controlled safety data:

The phase 3 study, B3461028 - a 30-month, randomized, double-blind, placebo-controlled study (tafamidis 20 mg, tafamidis 80 mg and placebo), serves as the primary source of safety data to compare the safety profile of tafamidis versus placebo in subjects with ATTR-CM.

Uncontrolled data in subjects with ATTR-CM:

- Study B3461045, an ongoing long-term safety extension study for phase 3 study B3461028 (cutoff date of 15 Feb 2018). Subjects who had been randomized to placebo in study B3461028 were randomized to either tafamidis 20 mg and 80 mg and subjects who had been randomized to tafamidis 20 mg or 80 mg continued on the same dose of tafamidis in the extension phase.
- Study B3461025, a 12 month, open-label, single arm (i.e. tafamidis 20 mg) and multicenter phase 2 study
- Study B3461026, an ongoing long-term safety extension study for phase 2 study B3461025

The uncontrolled safety data from these studies served a secondary role in my assessment of safety.

Safety data in subjects with ATTR-PN:

The applicant submitted clinical safety data and post-marking experience (cutoff date of 15 Jun 2018) in ATTR-PN patients as supportive safety data. The post-marketing experience includes a non-interventional study: Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS) with long-term, observational data on disease progression in patients with ATTR amyloidosis. Safety data in ATTR-PN patients were primary used to evaluate safety signals observed from ATTR-CM studies and assess the consistency of safety profile between the two development programs.

90-Day Safety Update:
A 90-day safety update was submitted on February 01, 2019. This safety update includes additional safety data in ongoing studies in ATTR-CM and ATTR-PN from 15 February 2018 to 01 August 2018, extending patient exposure to tafamidis in NDA 211996 by approximately 6 months. I primary used this additional data to update the deaths results in tafamidis groups in subjects with ATTR-CM.

Strategies to Assess Integrated Safety Data

Considering the differences between ATTR-PN and ATTR-CM programs (e.g. patient population, study duration, doses) and the absence of any ongoing controlled studies of tafamidis in ATTR-PN, the applicant has proposed separate safety data presentation for ATTR-PN and ATTR-CM. The Division agreed with this approach (written responses to the data proposals, April 12, 2018). The applicant subsequently proposed to analyze safety data in the ATTR-CM program based on different cohorts (e.g. health volunteer cohort, B3461028 cohort- the only controlled safety data, and all tafamidis cohort). The Division also agreed with the approach (meeting minutes to the type B meeting, August 15, 2018).

Primary Safety Analysis

The primary safety analysis used the safety set in the study B3461028- all patients who took at least one dose of study drug during the treatment period to assess the safety profile of tafamidis compared to placebo. The applicant has proposed several adverse events of special interest (AESIs) based on the findings from the ATTR-PN program and post-marketing experience, which includes diarrhea, upper abdominal pain, urinary tract infection, vaginal infection, hypersensitivity, hepatotoxicity, thyroid dysfunction, cardiac arrhythmia, central nervous system neoplasia, fall/dizziness/orthostatic hypotension, infection-related events and pancreatitis.

Other potential safety signals were also assessed by searching treatment-emergent adverse events (TEAEs) using all levels of MedDRA terms, standardized MedDRA query (SMQ) and ODE1 query. The common TEAEs that occurred in > 5% of patients treated with tafamidis with risk difference ≥ 2% and risk ratio ≥ 1.2 compared to the placebo group are “flagged” for further evaluation. Exposure-adjusted event rates (per 100 patient-years) were calculated for important safety signals of interest. Other safety assessments on laboratory evaluation, vital sign and ECG were also performed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The primary safety database came from the pivotal phase 3 study-B3461028 in patients with ATTR-CM (N = 88, 176 and 177 for the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively). Other supportive clinical trial data included safety experience in phase 1 healthy volunteer studies, a phase 2 single-arm study in ATTR-CM patients and safety data in ATTR-PN patients. Table 16 summarizes the main safety database for Tafamidis. Overall, a total of 377 ATTR-CM patients (including 78 placebo patients who received tafamidis during the extension phase of the phase 3 study) were exposed to tafamidis.

Table 16 Stafety Database for Tafamidis

Safety Database for Tafamidis Individuals exposed to any treatment in this development program for the indication under review N=1054[a]				
Clinical Trial Groups	Tafamidis[b] (n = 348)	Tafamidis 20 mg (n=222)	Tafamidis 80 mg (n= 176)	Placebo (n=308)
Healthy volunteers	348	---	---	71
Hepatic impairment	---	34	---	---
Controlled trials conducted for ATTR-CM (Phase 3- B3461028)	---	88	176	177[c]
All other trials conducted for ATTR-CM (Phase 2)	---	35	---	---
Controlled trials conducted for ATTR-PN (Phase 3-Fx-005)	---	65	---	63

a. In addition to the number of subjects listed in the table here, there were patients post-marketing data
b. In phase 1 heathy volunteer studies, one subject could receive more than one tafamidis dose, which includes dose other than 20 mg or 80 mg. For simplicity, total number of subjects who were exposed to tafamidis regardless of dose was listed here.
c. There were 27 and 51 placebo patients received tafamidis 20 mg and 80 mg respectively in the extension study.

In study B3461028, more than 65% of subjects in the tafamidis 20 mg and 80 mg groups were treated for 24 months or longer. The median exposure duration was 29.7, 29.8 and 27.9 months for tafamidis 20 mg, tafamidis 80 mg and placebo, respectively

Table 17 Study Drug Duration in the phase 3 study - B3461028

	Number of patients exposed to the study drug for selected duration category					
Dosage	< 6 months	6-<12 months	12-<18 months	18-<24 months	24-<30 months	30 <-36 months
Tafamidis 20 mg (N =88)	9 (10.2%)	3 (3.4%)	8 (9.1%)	4 (4.5%)	37 (42%)	38 (21.5%)
Tafamidis 80 mg (N=176)	13(7.4%)	19 (10.8%)	14 (8.0%)	11 (6.3%)	54 (30.7%)	65 (36.9%)
Placebo (N=177)	17 (9.6%)	17 (9.6%)	21(11.9%)	24 (13.6%)	60 (33.9%)	38 (21.5%)

90-Day Safety Update:
A 90-day safety update was submitted on February 01, 2019. This safety update includes additional safety data in ongoing studies in ATTR-CM and ATTR-PN from 15 February 2018 to 01 August 2018, extending patient exposure to tafamidis in NDA 211996 by approximately 6 months.

8.2.2. Relevant characteristics of the safety population:

Safety population is identical to the ITT population. Please refer to section 6.1.2 Table 6 in the efficacy review.

8.2.3. Adequacy of the safety database:

The size of safety database is acceptable and the characteristics of patients in the phase 3 study are generally similar to indicated US patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Jumpstart service provided data fitness evaluation for this NDA. The overall data and submission quality are reasonable. AE coding was evaluated using the Jumpstart output in which matching score was calculated comparing verbatim term to coded preferred term (PT). The AE coding is overall reasonable (Data Fitness outputs can be assess via http://sharepoint.fda.gov/orgs/CDER-OCS-JSRS5/SiteAssets/SharePoint%20FileTable.html by selecting NDA 211996).

8.3.2. Categorization of Adverse Events

All AEs were coded according to MedDRA and summarized by systemic organ class (SOC) and preferred term (PT) using MedDRA version 20.1. The applicant used standard procedures to collect and analyze AE data. AEs (both serious and non-serious) were recorded at all subject visits from the first dose through the last subject's last visit. The standard definition of SAE was used in the development program. TEAE is defined as an event which begins after start of treatment or which worsen during the course of the current study until the last dose +28 days. AESIs were pre-defined and the division agreed with the proposed definitions during the Type B Pre-NDA meeting (see MedDRA definitions for AESIs).

8.3.3. Routine Clinical Tests

The schedule for safety assessment in the phase 3 study can be found in Figure 6. Briefly, serum chemistry including standard parameters plus additional parameters specific to the program [i.e., retinol binding protein, total thyroxine (T4), free T4 and thyroid stimulating hormone (TSH)] was collect at each study visit. Blood and urine samples were collected at screening, baseline, week 2 (no urine), and at Months 1, 6,12,18,24, and 30. ECG assessments were performed at screening, baseline, Months 1, 6, 12, 18, 24 and 30. Overall, the safety assessments in tafamidis were acceptable.

8.4. Safety Results

8.4.1. Deaths

In the phase 3 study, CV-related deaths and non-CV related deaths were lower in both tafamidis groups compared to the placebo group (see section 6.1.2 for the mortality results). This finding is reassurance from the safety perspective.

The applicant has submitted 90-day safety update on February 01, 2019, which includes additional safety data with a cut-off date of 01 August 2018. Table 18 shows the overall mortality for ATTR-CM patients based on these updated safety data. There was a total of 39 (33.6%) deaths in the tafamidis 20 mg group and 71 (30.9%) in the tafamidis 80 groups. The death rate was particularly high among subjects who received placebo in the phase 3 study and then received tafamidis 20 mg during the extension phase. There was no difference in terms of death rates between tafamidis 20 mg and tafamidis 80 mg among subjects who received tafamidis since the beginning of the phase 3 study.

Table 18 Overall Mortality during the extension phase (cut-off date: 01 August 2018)

	Tafamidis 20 mg		Tafamidis 80 mg		Tafamidis 80 vs. 20 mg
	n/N (%)	ER[b]	n/N (%)	ER[b]	Hazard Ratio (95% CI)
Death (all causes)	39/116 (34%)	15.9	71/230 (31%)	14.5	0.9 (0.6,1.3)
Placebo-tafamidis	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 received placebo in the pivotal study and received either tafamidis 20 mg or 80 mg in the extension study
b. Event rate per 100 patient-years

Reviewer's Comment: The applicant stated that there is a trend in favor of tafamidis 80 mg vs. 20 mg for overall mortality based on data from the ongoing extension study. However, further evaluation of the data indicates that the difference is entirely driven by a small subset of patients who received placebo in the phase 3 study and then switched to tafamidis in the extension phase. Considering that the follow-up time (since tafamidis exposure) for this small subset is considerably shorter compared to the original cohort who started tafamidis at the beginning of the phase 3 study, the observed findings could be spurious. Overall, there is no strong clinical evidence suggesting a superior treatment effect of tafamidis 80 mg vs. 20 mg.

8.4.2. Serious Adverse Events

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.

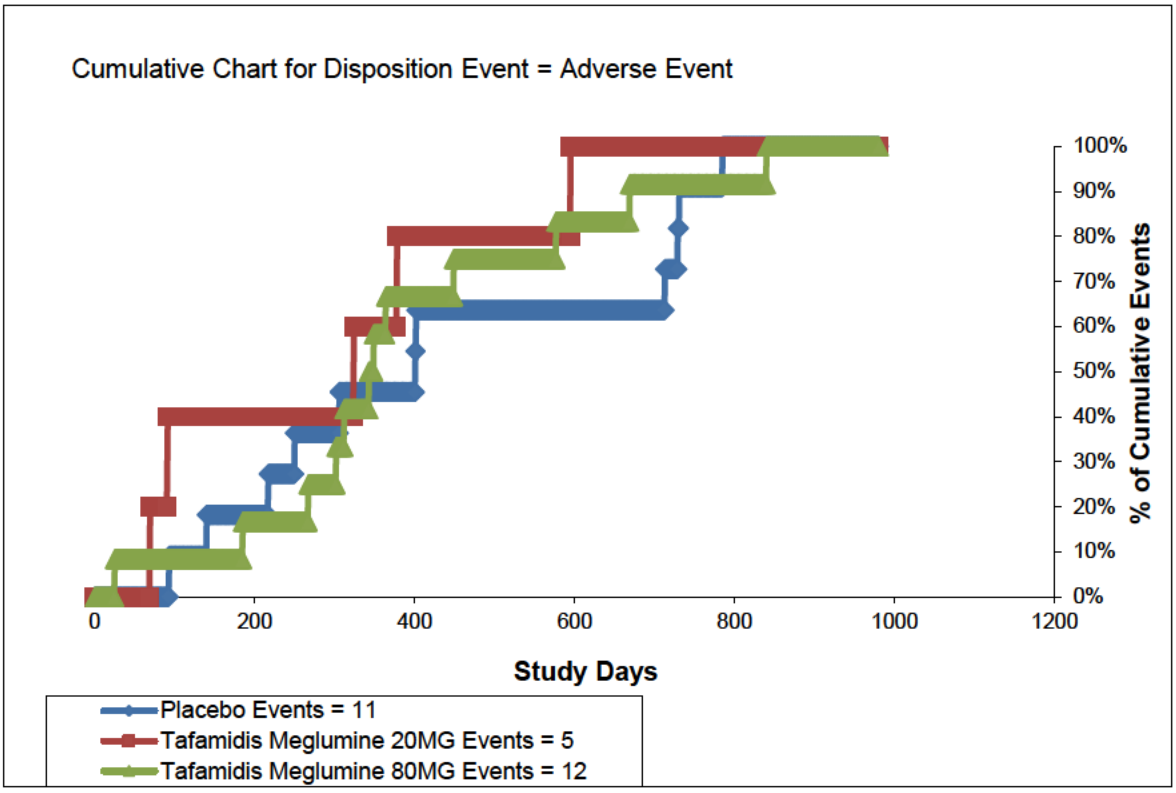
During the assessment of safety signals, it is noted that the frequency of SAEs for accident and injuries SMQ was higher in the tafamidis groups (11.4%) compared to the placebo (5.6%) group. Majority of these SAEs were fall-related injuries such as different types of fracture. This finding along with 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.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

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. 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.

> *Reviewer's Comment: The data presenting here is from the information recorded on the disposition case report form. The numbers do not include subjects who did not complete the study because of death. Majority of deaths were associated with the disease under study. There was no imbalance regarding other or unknown deaths leading to discontinuation among the treatment groups. Overall, the incidence of subjects who permanently withdrew due to an adverse event was fairly similar among the treatment groups.*

Figure 17 Cumulative distribution plot for time to disposition due to adverse event in the phase 3 study - B3461028



8.4.4. Significant Adverse Events

8.4.4.1 Adverse Events of Special Interest

The applicant has proposed several adverse events of special interest (AESIs) based on the findings from the ATTR-PN program and post-marketing experience. Table 19 summarizes the incidence of these events in study B3461028.

Table 19 Incidence of adverse events of special interest (AESI) in the phase 3 study -B3461028

AESI[a] (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. P	Risk Diff (%) T80 mg vs. P
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 (0%)	1 (0.6%)	0 (0%)	0	0.6

[a] The definition of each AESI was reviewed and agreed by the Division during the Pre-NDA Type B meeting see definitions for AESIs).

Overall, the frequency of these AEs was similar in the tafamidis groups compared to the placebo group. Further assessment of potential safety signals and selected safety topics of interest including infection/pneumonia, fall-related AEs, cataract, hepatotoxicity and thyroid dysfunction are summarized in the following sections.

8.4.4.2 Infection/pneumonia

Infection was one of the AESIs that the applicant identified from post-marketing experience. To further evaluate this signal, exposure-adjusted incidence rates were calculated. The incidence rate for all infection-related AEs was 39, 58 and 53 per 100 patient-years (per 100 pt-yrs) for the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively. The incidence rate is similar among the three treatment groups for serious infection-related AEs (Table 20).

Table 20 Exposure-adjusted incidence rate for infection-related AEs in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
All infection-related AEs (SOC: Infection and infestation)						
Placebo	177	203.78	109 (61.6)	53.49 (43.92, 64.53)		
Tafamidis Meglumine 20MG	88	126.68	49 (55.7)	38.68 (28.62, 51.14)	-14.81 (-29.58, -0.04)	0.72 (0.52, 1.01)
Tafamidis Meglumine 80MG	176	200.08	116 (65.9)	57.98 (47.91, 69.54)	4.49 (-10.08,19.05)	1.08 (0.83, 1.41)
Tafamidis 20 mg + 80 mg	264	326.76	165 (62.5)	50.50 (3.08, 58.82)	-2.99 (-15.65,9.66)	0.94 (0.74, 1.20)
Serious Infection-related AEs						
Placebo	177	311.59	37 (20.9)	11.87 (8.36, 16.37)		
Tafamidis Meglumine 20MG	88	172.35	19 (21.6)	11.02 (6.64, 17.22)	-0.85 (-7.11,5.41)	0.93 (0.53, 1.61)
Tafamidis Meglumine 80MG	176	332.93	32 (18.2)	9.61 (6.57, 13.57)	-2.26 (-7.34,2.81)	0.81 (0.50, 1.30)
Tafamidis 20 mg + 80 mg	264	505.28	51 (19.3)	10.09 (7.52, 13.27)	-1.78 (-6.51,2.94)	0.85 (0.56, 1.30)

A higher frequency of pneumonia was noted in both tafamidis groups compared to the placebo group. Table 21 shows the exposure-adjusted incidence rate for pneumonia. The incidence rate for pneumonia was 6.3, 8.0 and 5.6 per 100 pt-yrs for tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively. The incidence rate is similar among three treatment groups for serious pneumonia.

Table 21 Exposure-adjusted incidence rate for pneumonia-related AEs in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Infective pneumonia AEs (SMQ, narrow)						
Placebo	177	321.38	18 (10.2)	5.60 (3.32, 8.85)		
Tafamidis Meglumine 20MG	88	174.18	11 (12.5)	6.32 (3.15, 11.30)	0.71 (-3.83,5.26)	1.13 (0.53, 2.39)
Tafamidis Meglumine 80MG	176	339.66	27 (15.3)	7.95 (5.24, 11.57)	2.35 (-1.61,6.31)	1.42 (0.78, 2.58)
Tafamidis 20 mg + 80 mg	264	513.84	38 (14.4)	7.40 (5.23, 10.15)	1.79 (-1.70,5.29)	1.32 (0.75, 2.31)
Infective pneumonia SAEs (SMQ, narrow)						
Placebo	177	326.65	13 (7.3)	3.98 (2.12, 6.18)		
Tafamidis Meglumine 20MG	88	180.91	6 (6.8)	3.32 (1.22, 7.22)	-0.66 (-4.09,2.76)	0.83 (0.32, 2.19)
Tafamidis Meglumine 80MG	176	350.24	14 (8.0)	4.00 (2.19, 6.71)	0.02 (-2.99,3.03)	1.00 (0.47, 2.14)
Tafamidis 20 mg + 80 mg	264	531.16	20 (7.6)	3.77 (2.30, 5.82)	-0.21 (-2.94,2.51)	0.95 (0.47, 1.90)

Reviewer's Comment: Although the incidence rate of overall infection or pneumonia is numerically higher in the tafamidis 80 mg group compared to the placebo group, the difference is modest, and the overall findings do not suggest that tafamidis is related to the risk of having an infection even though there were some signals detected in the ATTR-PN program.

In the phase 3 study in patients with ATTR-PN, an infection occurred in 68% of subjects in the tafamidis 20 mg group vs. 52% in the placebo group. The most common infection in the ATTR-PN program was urinary tract infection (UTI) with 23% and 14% in the tafamidis 20 mg and placebo groups, respectively. It is possible that this safety signal is unique to the ATTR-PN population because of their greater risk due to autonomic dysfunction. Alternatively, the observed imbalance in the ATTR-PN study, a smaller study (n = 65 and 63 in the tafamidis 20 mg and placebo groups, respectively) with a shorter duration (i.e. 18-month follow up) could be spurious.

It is also noted that the infection rate is particularly low in the tafamidis 20 mg group compared to the tafamidis 80 and placebo groups. This finding supports that infection AEs are likely not related to tafamidis.

8.4.4.3 Fall-related AEs

Some fall-related safety signals were detected during the assessment include the individual PT-balance disorder, fall and the SMQ query- accidents and injuries (Table 22).

Table 22 Safety signals related to balance disturbances/fall/injuries in study B3461028[a]

	Tafamidis 20 mg (N = 88)	Tafamidis 80 mg (N = 176)	Placebo (N = 177)	Risk Diff T20 mg vs. P	Risk Diff T80 mg vs. P
Coordination and balance disturbances (HLT)	2 (2.3%)	16 (9.1%)	3 (1.7%)	0.6	7.4
balance disorder	2 (2.3%)	15 (8.5%)	2 (1.1%)	1.2	7.4
Fall (ODEI-query)	27 (30.7%)	43 (24.4%)	41 (23.2%)	7.5	1.3
Accident and injuries (SMQ), narrow	37 (42%)	62 (35.2%)	59 (33.3%)	8.7	2.0
Accident and injuries (SMQ), narrow-SAE*	10 (11.4%)	20 (11.4%)	10 (5.6%)	5.8	5.8

* Signal is driven by fall and fractures

[a] Data presented at the safety scoping meeting

After reviewing the narratives, almost all serious accidents and injuries (e.g. fracture) were fall-related injuries except injuries related to traffic accidents. It is also noted that there are no safety signals for AEs such as dizziness, dizziness postural and hypotension. The vital sign data also do not suggest a signal for orthostatic hypotension (see section 8.4.7). To further consolidate and evaluate these signals, we re-grouped PTs and included ataxia, balance disorder, gait disturbance, fall and serious accident and injuries SMQ (excluding road traffic accident). Table 23 shows the frequency and exposure-adjusted incidence rate for fall-related AEs.

Table 23 Exposure-adjusted incidence rate for fall-related AEs in study B3461028

	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	283.60	49 (27.7)	17.28 (12.78, 22.84)		
Tafamidis Meglumine 20MG	88	157.12	29 (33.0)	18.46 (12.36, 26.51)	1.18 (-7.10,9.46)	1.07 (0.67, 1.69)
Tafamidis Meglumine 80MG	176	301.40	53 (30.1)	17.58 (13.17, 23.00)	0.31 (-6.46,7.08)	1.02 (0.69, 1.50)
Tafamidis 20 mg + 80 mg	264	458.53	82 (31.1)	17.88 (14.22, 22.20)	0.61 (-5.59,6.80)	1.04 (0.73, 1.47)
Fall-related SAEs						
Placebo	177	330.78	9 (5.1)	2.72 (1.24, 5.16)		
Tafamidis Meglumine 20MG	88	175.67	10 (11.4)	5.69 (2.73, 10.47)	2.97 (-0.98,6.92)	2.09 (0.85, 5.15)
Tafamidis Meglumine 80MG	176	345.63	20 (11.4)	5.79 (3.53, 8.94)	3.07 (-0.03,6.16)	2.13 (0.97, 4.67)
Tafamidis 20 mg + 80 mg	264	521.31	30 (11.4)	5.75 (3.88, 8.22)	3.03 (0.31,5.75)	2.12 (1.00, 4.45)

After re-grouping the relevant PTs, the incidence rate was similar among the treatment groups. However, the risk of having fall SAEs was about doubled in the tafamidis groups vs. placebo group. Theses serious events represent falls with serious injuries (e.g. fracture, head injury).

Reviewer's Comment: The finding that fall SAEs are more frequently occurred in the tafamidis groups compared to the placebo group is not exactly clear. Based on AEs and vital sign data (section 8.4.7), there are no clear mechanisms (e.g. no signal for hypotension or postural hypotension). The imbalance in SAEs could be due to chance or the fact that subjects in the tafamidis groups felt better with more mobilities thus had a higher probability for an actual fall. Nevertheless, falls in this patient population or elderly in general are not uncommon and could result in devastating outcomes. There was no signal for fall-related AEs in the ATTR-PN program. The clinical trial data is limited to conclude the association between tafamidis and fall.

8.4.4.4 Cataract

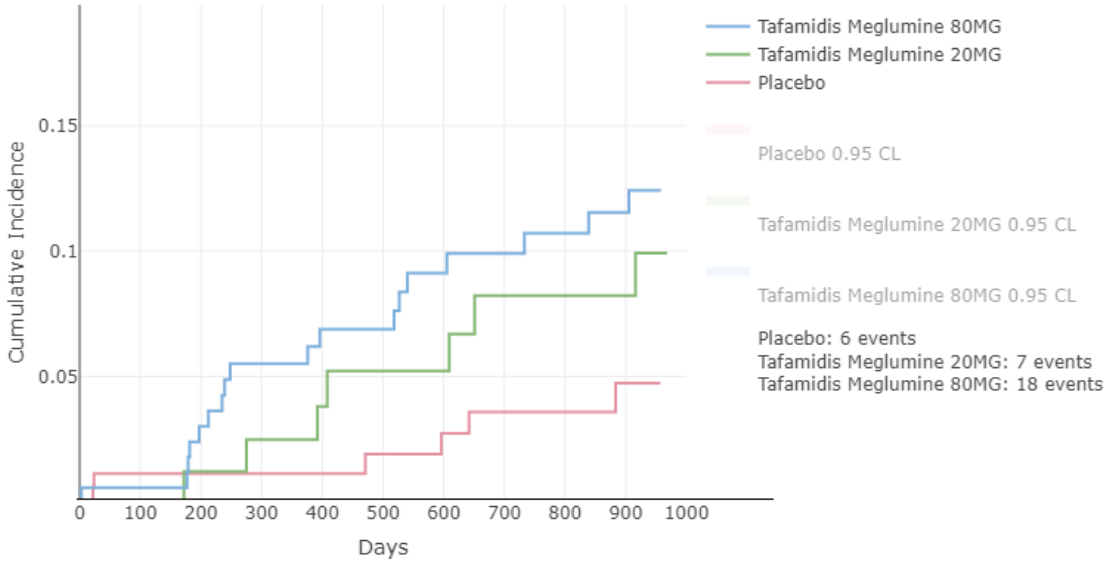
There was a higher incidence of cataract and other visual related AEs based on lens disorder (SMQ) in the tafamidis groups vs. placebo. This safety signal is primary driven by the imbalance in cataract AE-3/88 (3%), 9/176 (5%), and 2/177 (1%) in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively. Table 24 shows the exposure-adjusted incidence rate for these vision-related AEs. The risk of having these events was more than double in the tafamidis groups compared to the placebo. The Kaplan-Meier curves (Figure 18) show that the lines started separating at around 200 days of the study.

Table 24 Exposure-adjusted incidence rate for lens disorder (SMQ) in in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Lens disorder (SMQ)[a]						
Placebo	177	328.11	6 (3.4)	1.83 (0.67, 3.98)		
Tafamidis Meglumine 20MG	88	176.67	7 (8.0)	3.96 (1.59, 8.16)	2.13 (-1.15,5.41)	2.17 (0.73, 6.45)
Tafamidis Meglumine 80MG	176	341.26	18 (10.2)	5.27 (3.13, 8.34)	3.45 (0.60,6.29)	2.88 (1.14, 7.27)
Tafamidis 20 mg + 80 mg	264	517.93	25 (9.5)	4.83 (3.12, 7.13)	3.00 (0.61,5.39)	2.64 (1.08, 6.43)

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

Figure 18 The Kaplan-Meier Curves for AEs in lens disorder (SMQ)



Reviewer's Comment: Based on this observed safety signal, we submitted a consult request to the Division of Transplant and Ophthalmology Products (DTOP) on January 17, 2019 to ask the DTOP's input on whether this signal could be drug-related. The consult review was completed on February 12, 2019. 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.

8.4.4.5 Hepatotoxicity

Nonclinical studies have shown some tafamidis-associated hepatic alterations at exposure approximately ≥ 0.7 times the human exposure at a dose of 61 mg tafamidis and 2.5-times the human exposure at a dose of 20 mg tafamidis. Although the mechanism for those findings is not clear, hepatoxicity is considered a potential risk for tafamidis and is one of the AESIs identified for evaluation in the development program.

Using the MedDRA SMQ of drug-related hepatic disorder (narrow scope), there was no imbalance regarding hepatotoxicity-related AE (Table 25). Further assessment of this signal reveals that majority of AEs were elevated liver enzymes (11%, 10% and 6% in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively) and increased international normalized ratio (6%, 2% and 3% in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respective).

Table 25 Exposure-adjusted incidence rate for Hepatoxicity in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Hepatoxicity[a]						
Placebo	177	298.07	39 (22.0)	13.08 (9.30, 17.89)		
Tafamidis Meglumine 20MG	88	160.03	23 (26.1)	14.37 (9.11, 21.57)	1.29 (-5.88,8.46)	1.10 (0.66, 1.84)
Tafamidis Meglumine 80MG	176	314.11	38 (21.6)	12.10 (8.56, 16.61)	-0.99 (-6.61,4.64)	0.92 (0.59, 1.45)
Tafamidis 20 mg + 80 mg	264	474.14	61 (23.1)	12.87 (9.84, 16.53)	-0.22 (-5.44,5.01)	0.98 (0.66, 1.47)

[a] MedDRA SMQ for drug-related hepatic disorder (narrow scope)

There were two SAEs associated with elevated liver enzymes; one case was in the tafamidis 20 mg group and the other case was in the tafamidis 80 mg.

Reviewer's Comment: The AE findings are consistent with the laboratory results which indicate some signals for tafamidis-associated liver enzyme elevations (section 8.4.6.2). Despite of these laboratory changes, there is no corresponding clinical evidence of hepatoxicity in the ATTR-CM and ATTR-PN development program. The applicant also monitored and evaluated hepatoxicity in the post-marketing setting including safety data from an observational study- THAOS (see section 8.8.1). It is noted that there was one possible hepatic event associated with tafamidis; however, the causal association cannot be concluded based on the available data thus far. Overall, hepatoxicity remains a potential risk for tafamidis and potential hepatic events occurred in the post-marketing setting should be tracked.

8.4.4.7 Thyroid Dysfunction and asthenic condition

There is a theoretical risk of thyroid function abnormalities for tafamidis based on its mechanism of action. The applicant has identified thyroid dysfunction as an AESI and assessed relevant laboratory measurements (i.e. TSH, T4 and free T4) (see section 8.4.6.1). Using the MedDRA SMQ for thyroid dysfunction and MedDRA HLT for asthenic condition, we did not find a signal of concern for clinical thyroid dysfunction (Table 26).

Table 26 Exposure-adjusted incidence rate for thyroid dysfunction in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Thyroid dysfunction (MedDRA SMQ)						
Placebo	177	311.66	19 (10.7)	6.10 (3.67, 9.52)		
Tafamidis Meglumine 20MG	88	179.42	6 (6.8)	3.34 (1.23, 7.28)	-2.75 (-6.58,1.08)	0.55 (0.22, 1.37)
Tafamidis Meglumine 80MG	176	344.46	16 (9.1)	4.64 (2.66, 7.54)	-1.45 (-5.01,2.11)	0.76 (0.39, 1.48)
Tafamidis 20 mg + 80 mg	264	523.87	22 (8.3)	4.20 (2.63, 6.36)	-1.90 (-5.15,1.36)	0.69 (0.37, 1.27)
Asthenic condition (MedDRA HLT)						
Placebo	177	279.75	42 (23.7)	15.01 (10.82, 20.29)		
Tafamidis Meglumine 20MG	88	153.38	21 (23.9)	13.69 (8.48, 20.93)	-1.32 (-8.73, 6.09)	0.91 (0.54, 1.54)
Tafamidis Meglumine 80MG	176	309.70	45 (25.6)	14.53 (10.60, 19.44)	-0.48 (-6.70, 5.73)	0.97 (0.64, 1.47)
Tafamidis 20 mg + 80 mg	264	463.07	66 (25.0)	14.25 (11.02, 18.13)	-0.76 (-6.46, 4.93)	0.95 (0.64, 1.40)

Concomitant medication use for hypothyroidism in the phase 3 study was also evaluated. There were 13.6%, 23%, and 18% of subjected 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% & 6.5% in the tafamidis 80 mg, tafamidis 20 mg and placebo groups, respectively.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The overall occurrence of treatment-emergent adverse events (TEAEs) was similar among the treatment groups (Table 27). Pre-defined AESIs and selected safety topics were evaluated and discussed in section 8.4.4; none of them indicate a strong safety signal of concern and/or show a clear tafamidis-associated adverse reactions.

Table 27 Incidence of treatment-emergent AEs in study B3461028

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)

8.4.6. Laboratory Findings

In general, analyses of the laboratory data did not raise any major safety concerns. Laboratory parameters of interest are discussed further below.

8.4.6.1 Thyroxine and Retinol Binding Protein

TTR is a transport protein for thyroxin and retinol binding protein-vitamin A complex (RBP). There is a theoretical risk that tafamidis may have some impacts on RBP and thyroxine hormone levels, particularly the latter, as tafamidis binds to the thyroxine binding site of TTR. In the phase 3 trial, there was a notable decrease in T4 and free T4 in the tafamidis groups starting

at week 2 throughout the end of the study (Figure 19 and Figure 20). However, there were no meaningful changes for TSH and RBP across time in the study (Figure 21 and Figure 22).

Figure 19 Mean Thyroxine (T4) across time in study B3461028

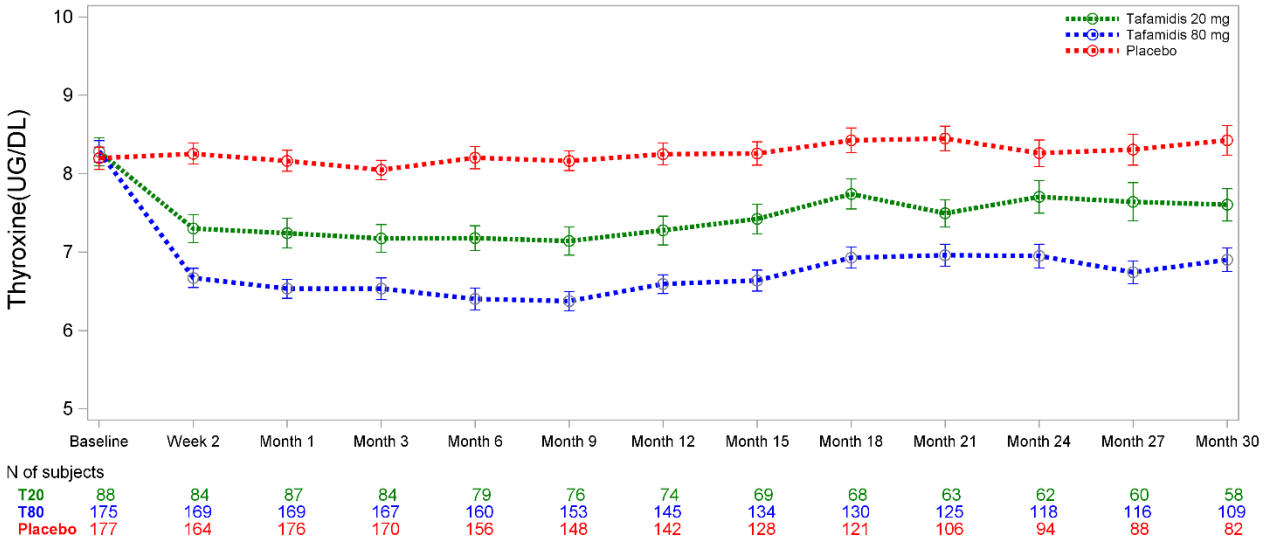


Figure 20 Mean Free Thyroxine (free T4) across time in study B3461028

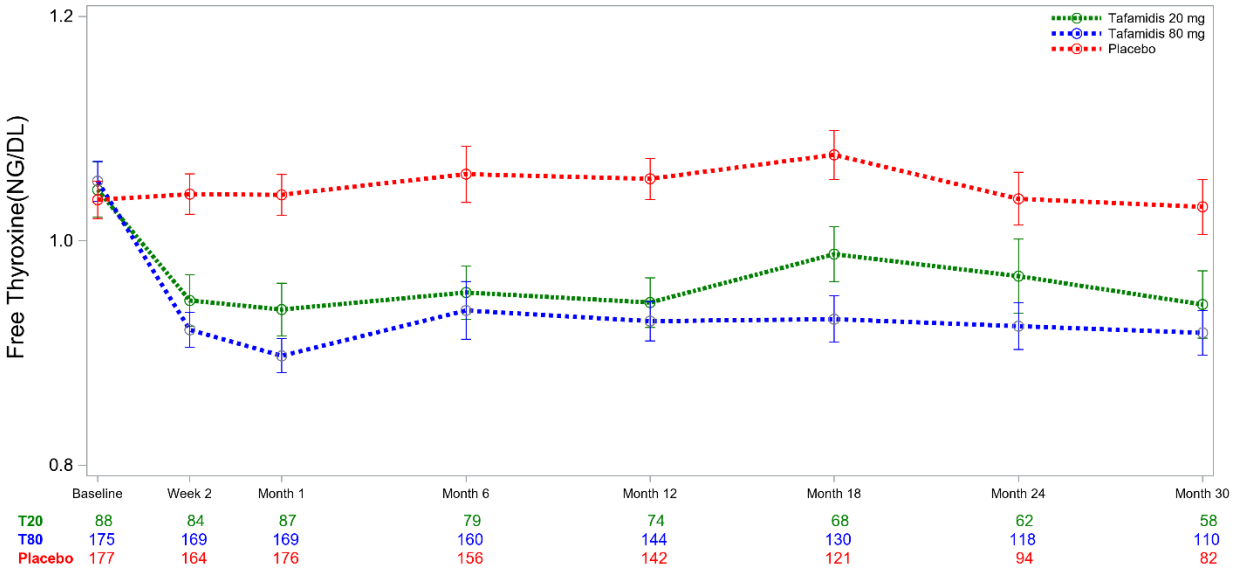


Figure 21 Mean Thyrotropin (thyroid stimulating hormone) across time in study B3461028

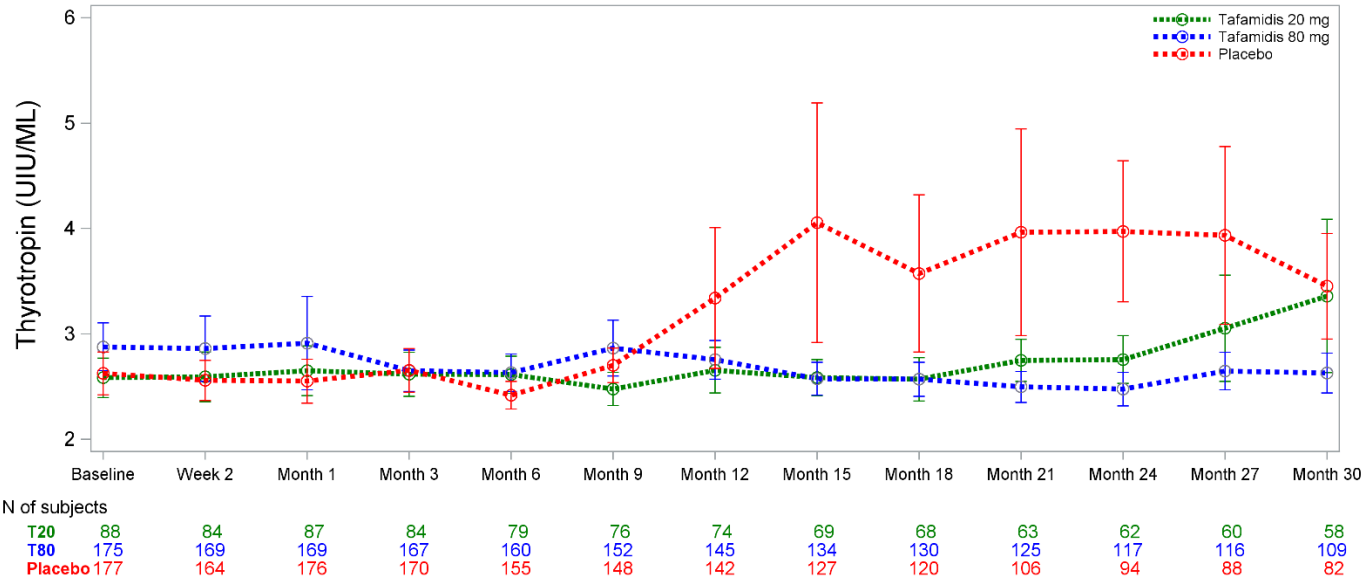


Figure 22 Mean Retinol Binding Protein across time in study B3461028

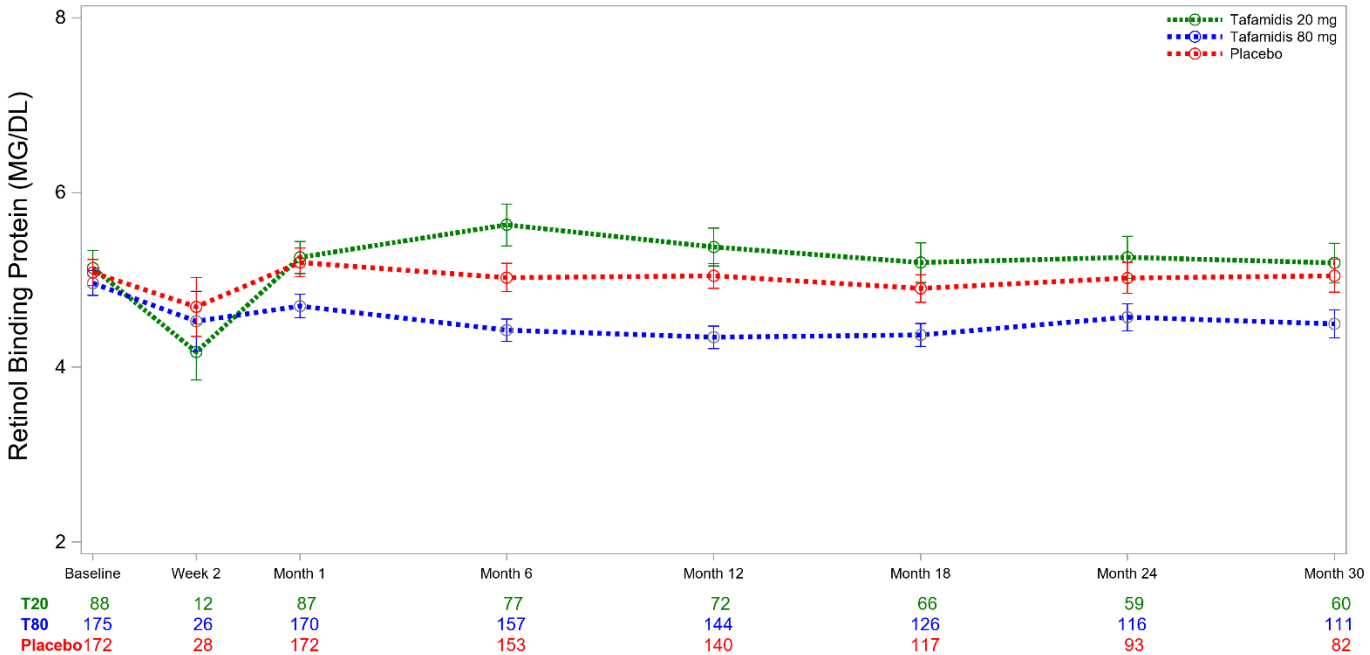


Table 28 shows the incidence of abnormalities for T4, Free T4, TSH and RBP in serum. The most notable imbalance was that a higher percentage of subjects in the tafamidis groups had T4 values < 0.8 XLLN (14% and 33% in the tafamidis 20 mg and tafamidis 80 mg groups respectively) compared to the placebo group (7%). This finding is in general consistent in clinical subgroups of interest (i.e. TTR genotype and NYHA class).

Table 28 Incidence of laboratory abnormalities in study B3461028[a]

Laboratory abnormalities	*Tafamidis 20MG N=88 n (%)*	*Tafamidis 80MG N=176 n (%)*	*Placebo N=177 n (%)*
T4 < 0.8 LLN	12 (13.6)	58 (33.0)	12 (6.8)
T4 >1.2 ULN	1 (1.1)	1 (0.6)	2 (1.1)
TSH < 0.8 LL	2 (2.3)	16 (9.1)	8 (4.5)
TSH >1.2 ULN	12 (13.6)	29 (16.5)	32 (18.1)
Free T4 < 0.8 LL	0(0)	2 (1.1)	3 (1.7)
Free T4 >1.2 ULN	21 (23.9)	43 (24.4)	60 (33.9)
RBP < 3mg/dL	18 (21)	59 (34)	47 (27)
RBP > 6mg/dL	45 (51)	77 (44)	90 (51)

[a] The incidence is calculated from all safety population regardless abnormality status at baseline

Reviewer's Comment: The laboratory data indicate that tafamidis is associated with a decrease in T4 and the changes seem dose-dependent. Similar time course changes were also observed in free T4 but the magnitude of the changes is small and the clinical relevance of this finding is not clear. There were minimal tafamidis-associated changes regarding TSH levels and RBP. In human plasma, thyroxine binding globulin is the primary carrier protein of plasma thyroxine and TTR only accounts for ~10% to 20% of protein bound plasma thyroxin and only <1% of TTR transporting thyroxine. Given that there are minimal changes in TSH and the absence of corresponding clinical thyroid dysfunction AEs (section 8.4.4.7), it is likely that that normal thyroid function was maintained in subjects treated with tafamidis.

8.4.6.2 Liver enzymes

The incidence of subjects and event count for abnormal Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) and Total Bilirubin (TB) greater at 2x, 3x, 5x, 10x, and 20x upper limit of normal (ULN)post-baseline were summarized in Table 29. Overall, the incidence of abnormal liver function tests was low but there were more subjects in the tafamidis 80 mg group with ALT or AST ≥3x ULN compared to the placebo group.

Table 29 Abnormal liver enzymes in study B3461028

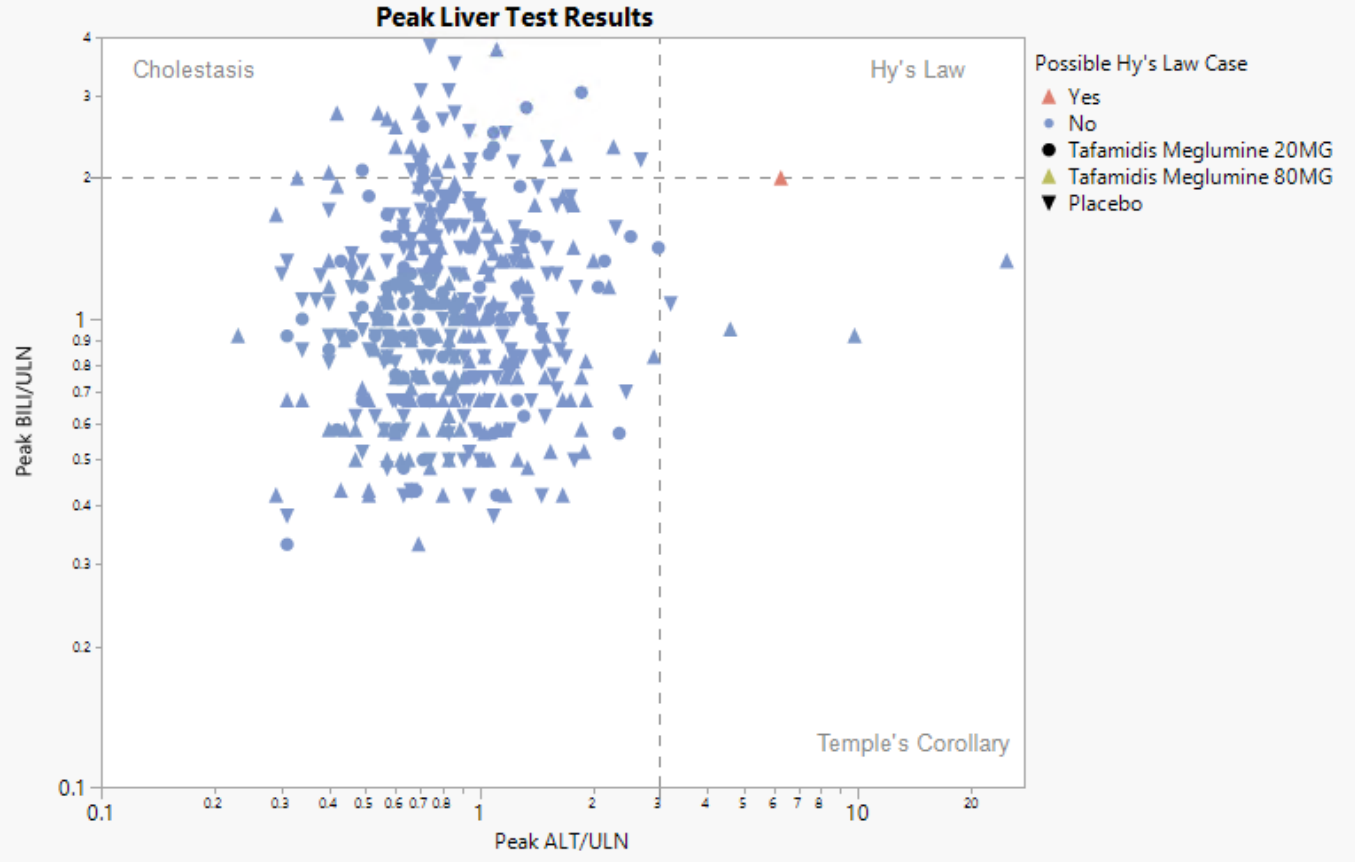
Liver Lab Test	Tafamidis Meglumine 20MG N = 88			Tafamidis Meglumine 80MG N = 176			Placebo N = 177		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	6	5	5.68	8	8	4.55	5	4	2.26
3x ULN	0	0	0.00	4	4	2.27	1	1	0.56
5x ULN	0	0	0.00	3	3	1.70	0	0	0.00
10x ULN	0	0	0.00	1	1	0.57	0	0	0.00
20x ULN	0	0	0.00	1	1	0.57	0	0	0.00
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	3	3	3.41	16	13	7.39	17	8	4.52
3x ULN	1	1	1.14	6	5	2.84	0	0	0.00
5x ULN	0	0	0.00	1	1	0.57	0	0	0.00
10x ULN	0	0	0.00	1	1	0.57	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	16	5	5.68	26	11	6.25	63	16	9.04
3x ULN	0	0	0.00	1	1	0.57	6	3	1.69
5x ULN	0	0	0.00	0	0	0.00	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00	0	0	0.00
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	25.00	133	36	20.45	141	45	25.42
2x ULN	26	10	11.36	44	17	9.66	42	15	8.47
3x ULN	1	1	1.14	3	1	0.57	11	4	2.26

Notes: All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (i.e., 2x, 3x, 5x…) that apply.

Combined abnormalities (ALT or AST ≥ 3 ULN, TB ≥ 2 ULN) at the same visit were assessed for possible Hy's law cases (Figure 23). There was 1 possible Hy's law case (subject [redacted] (b) (6)) in the tafamidis 80 mg and none in the tafamidis 20 mg or placebo groups. Combined abnormalities were also assessed at any time in the phase 3 study (abnormal values did not need to occur at the same visit). Using this broader criterion, there was an additional possible Hy's law case (subject [redacted] (b) (6)). The narrative of these two cases is described at the end of this section.

There were few patients in the tafamidis 80 mg group with elevated ALT or AST meeting criteria for Temple's corollary (Figure 23). The elevated liver enzymes in these patients were single occurrences at varying timepoints and were back to normal ranges while on treatment except for one case (subject [redacted] (b) (6)). The narrative of this subject is described at the end of this section.

Figure 23 Hy's Law Quadrant in study B3461028 (possible Hy's low cases are flagged if ALT or AST≥ 3 ULN and TB ≥ 2 ULN within 0 days of ALT/AST elevation)



Narratives for 2 potential Hy's law cases based on liver chemistries in the tafamidis 80 mg group

Subject (b) (6): This case occurred in a 75-year-old white male (NIHA class III) who had a history of atrial fibrillation, hyperlipidemia, hypertension and chronic kidney disease. The patients had a complete atrioventricular (AV) block complicated by hypotension about one month after treatment of tafamidis 80 mg. He was hospitalized and had a pacemaker implanted on the same day. During hospitalization, laboratory test showed elevated creatinine and liver enzymes. The patient's condition improved gradually, and the laboratory abnormalities were resolved. The patient was discharged from hospital after 5 days. The patient continued on treatment of tafamidis for about 2 years and his liver enzymes were within normal range during the study.

Subject (b) (6): This case occurred in a 74-year-old black male (NIHA class III) who had an ongoing medical history of cardiac failure, chronic obstructive pulmonary disease (COPD), dyspnea and dyslipidemia. On study day 465 (~ 15 month on study treatment), AEs of elevated liver abnormalities and progression of worsening chronic lung condition were reported. Elevated liver abnormalities were coded recovered/resolved in the AE database but there was no additional measurements of liver enzymes after the AE. On day 496, the study drug was permanently discontinued due to worsening dyspnea. The patient was hospitalized on the same day. He was recommended to go on home hospice care due to his poor prognosis and his end stage of COPD. The patient died due to end stage of COPD about 1 year after withdrawal from the study.

Narrative for a subject with elevated ALT/AST in the tafamidis 80 mg group

Subject (b) (6): This case occurred in an 82-year-old black male (NYHA class III) who had a past medical history of congestive cardiac failure, coronary angioplasty and implantable defibrillator placement. On study day 8, he had elevated ALT/AST (> 10x UNL) and normal ALP and BILI (his BILI did not change from baseline and was slightly higher than ULN but lower than 1.5x ULN). He was hospitalized due to congestive cardiac failure on study day 9 and the study drug was permanently discontinued due to this event with the last dose taken on study day 8. There were no available laboratory measurements after this event. The patient underwent a coronary angioplasty on study day 12 and he discontinued the study due to the event of congestive cardiac failure on study day 25. He was hospitalized due to cardiomyopathy on study day 28 and the patient died due to cardiomyopathy assessed as caused by disease under study on day 38.

Reviewer's comment: The two potential Hy's law cases were not consistent with drug-induced liver injury. For the first case, the combined liver abnormalities were likely due to

the event of AV block complicated by hypotension; for the second case, the subject had normal ALT/AST during treatment for more than 1 year and had combined liver abnormalities at the last visit when he also experienced worsening medical conditions including worsening dyspnea/ heart failure/COPD exacerbation. It is likely that the event of liver abnormalities was secondary to patient's cardiac disease. I am more concerned about the last case who had marked elevations of ALT/AST after 8 days of treatment. Although it's very likely that the increases of serum AT were due to ischemic hepatitis secondary to heart failure, the potential risk for tafamidis-associated hepatocellular injury cannot be ruled out due to the supportive temporal relationship.

Assessing hepatoxicity in ATTR-CM patients is challenging because the elevated transaminases are likely confounded by patients' cardiovascular diseases. Given the totality data available to date, there is insufficient evidence to conclude the association but hepatoxicity remains a potential risk for tafamidis.

8.4.6.3 Other laboratory parameters

There were no meaningful differences between the treatment arms for other laboratory parameters (see creatinine in section 6.1.2).

8.4.7. Vital Signs

Overall, there were no meaningful differences between the treatment groups in terms of mean vital signs across time and categorical changes of vital sign from baseline. Orthostatic hypotension was also evaluated in the phase 3 study with the definition listed below:

- Supine systolic blood pressure (SBP) - Standing SBP ≥ 20 mmHg, or
- Supine diastolic blood pressure (DBP) – Standing DBP ≥ 10 mmHg, or
- Standing pulse-supine pulse > 20 bpm along with standing pulse or supine pulse > 100 bpm

The incidence of orthostatic hypotension is similar among the three treatment groups (Table 30). Consistent with the findings from AE data, there is no apparent evidence indicating the risk of orthostatic hypotension.

Table 30 Incidence of orthostatic hypotension in study B3461028

Study Visit	Tafamidis 20 mg (N=88) %(n/N)	Tafamidis 80 mg (N=176) %(n/N)	Placebo (N=177) %(n/N)
Baseline	11.4 (10/88)	13.6 (24/176)	10.2 (18/177)
Anytime On-Treatment	52.9 (46/87)	46.8 (81/173)	50.0 (88/176)
Month 1	10.3 (9/87)	8.5 (14/165)	13.6 (24/176)
Month 3	10.7 (9/84)	9.6 (16/167)	13.5 (23/170)
Month 6	11.4 (9/79)	13.7 (22/161)	10.8 (17/158)
Month 9	16.9 (13/77)	7.1 (11/155)	10.7 (16/149)
Month 12	13.5 (10/74)	12.5 (18/144)	13.3 (19/143)
Month 15	5.9 (4/68)	7.4 (10/135)	8.7 (11/126)
Month 18	10.3 (7/68)	8.5 (11/129)	7.3 (9/123)
Month 21	12.7 (8/63)	9.8 (12/123)	10.3 (11/107)
Month 24	11.3 (7/62)	13.4 (16/119)	10.2 (10/98)
Month 27	14.8 (9/61)	13.0 (15/115)	6.7 (6/89)
Month 30	11.7 (7/60)	12.6 (14/111)	15.7 (13/83)

8.4.8. Electrocardiograms (ECGs)

Mean change of ECG parameters from baseline to each post-baseline time point (at 1, 6, 12, 18, 24, and 30 months) was reported. The time-course data did not show meaningful differences in QTcF, QTcB, QRS duration and PR interval among treatment arms. Table 31 presents the categorical analysis of each ECG parameter.

Table 31 The categorical analysis of ECG parameters for study B3461028

	Tafamidis_20mg n/N[a] (%)	*Tafamidis_80mg n/N[a] (%)*	*Placebo n/N[a] (%)*
HR> 100 bpm	9/87 (10.3)	7/171 (4.1)	10/173 (5.8)
HR< 60 bpm	29/87 (33.3)	62/171 (36.3)	61/173 (35.3)
PR >200 msec	35/40 (87.5)	72/86 (83.7)	63/77 (81.8)
PR >240 msec	16/40 (40.0)	46/86 (53.5)	36/77 (46.8)
PR change >25% increase from baseline	8/40 (20.0)	12/86 (14.0)	13/77 (16.9)
QRS >110 msec	69/87 (79.3)	136/171 (79.5)	140/171 (81.9)
QRS >120 msec	64/87 (73.6)	125/171 (73.1)	124/171 (72.5)
QRS change >25% increase from baseline	21/87 (24.1)	37/171 (21.6)	40/171 (23.4)
QTcF >450 msec	80/86 (93.0)	158/171 (92.4)	156/171 (91.2)
QTcF >500 msec	38/86 (44.2)	77/171 (45.0)	72/171 (42.1)
30 <ΔQTcF[b] <=60 msec	34/86 (39.5)	57/171 (33.3)	50/171 (29.2)
Δ QTcF[b] >60 msec	6/86 (7.0)	18/171 (10.5)	24/171 (14.0)
QTcB >450 msec	83/86 (96.5)	165/171 (96.5)	164/171 (95.9)
QTcB >500 msec	50/86 (58.1)	104/171 (60.8)	104/171 (60.8)
30 < ΔQTcB[b] <=60 msec	39/86 (45.3)	61/171 (35.7)	65/171 (38.0)
ΔQTcB[b] >60 msec	12/86 (14.0)	18/171 (10.5)	26/171 (15.2)

[a] The denominator is number of patients who had baseline and at least 1 post-baseline measurement for the corresponding ECG parameter. The numerator indicates number of patients who had at least 1 post-baseline measurements met the criterion for corresponding ECG parameter
[b] Change from baseline

Reviewer's Comment: It is noted that a significant portion of subjects did not have available PR interval either at pre- or post-baseline. However, the missingness of the PR interval is similar among the treatment groups. Overall, ECG data did not reveal a major safety concern.

8.4.9. QT

The FDA QT Interdisciplinary review team reviewed the Thorough QT study (Study B3461031). According to their review (DARRT under IND 71880 in January 2014), there were no detectable prolongations of the QT-interval at the supratherapeutic dose of tafamidis 400 mg in healthy subjects (n = 42). There were also no clinical meaningful findings for HR, PR and QTS interval in the study.

8.4.10. Immunogenicity

There is a theoretical immunogenicity risk for tafamidis based on a putative association of acylglucuronide metabolites and idiosyncratic adverse drug reaction. Hence, hypersensitivity is one of the AESIs that the applicant identified and assessed throughout the development program. There was no imbalance among the treatment groups based on the AE search for the narrow scope of hypersensitivity SMQ (see Table 19).

The applicant also extended the search by including additional MedDRA terms: asthma/bronchospasm (broad and narrow scope); and the additional breathing difficulty/abnormalities PTs: apneic attack, dyspnea, dyspnea at rest, dyspnea exertional, dyspnea paroxysmal nocturnal, hypoventilation, irregular breathing, nocturnal dyspnea, respiration abnormal, respiratory distress and upper airway resistance syndrome. This broader search also did not indicate a safety signal. The frequency of developing these events was 32%, 35% and 45% in the tafamidis 20 mg, tafamidis 80 mg and placebo group, respectively. Overall, no signal emerged from the ATTR-CM clinical studies regarding immunological events.

8.5. Analysis of Submission-Specific Safety Issues

There are no specific safety issues have been submitted except AESIs (section 8.4.4) and reproductive toxicity (section 8.7.2).

8.6. Safety Analyses by Demographic Subgroups

Overall, we did not identify a particular safety concern from AE data that warrant a subsequent evaluation of subgroups. In addition, majority of subjects in the phase 3 study are elderly white males, which preclude the exploratory analyses by demographic subgroups.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Intracranial neoplasm was a safety signal that had been evaluated and discussed in the development program. There were four SAE reports of intracranial neoplasm in ATTR-PN clinical studies and the applicant has identified it as an AESI and evaluated this safety signal in the ATTR-CM development program. Safety data regarding intracranial neoplasm have been reviewed by the external Data Monitoring Committee (DMC) and there were no significant concerns raised in view of negative carcinogenic effect in animals and rare and non-specific nature of these events. There were 0 intracranial neoplasm case in the phase 3 trial in patients with ATTR-CM and a total of 1 case in the ATTR-CM clinical development program. The case is a 73-year old white male patient participated the phase 2 study and had an SAE of glioblastoma multiforme after presenting with cognitive deficits during the extension phase (study day 348) (see the narrative).

During the safety assessment, it was also noted that higher frequency of malignant tumor (SMQ) AEs occurred in the tafamidis 80 mg group compared to the placebo group. Majority of these AEs are skin cancers including basal cell carcinoma, squamous cell carcinoma and melanoma. A similar signal is also detected by ODE-1 query for solid neoplasia (benign, malignant, unknown). Table 32 shows the exposure-adjusted incidence rate for malignant tumors. There was no clear pattern about the timing of these events. The events occurred sporadically throughout the study.

Table 32 Exposure-adjusted incidence rate for malignant tumor in study B3461028

	N	Subject-years of exposure	n (%)	Incidence Rate (95% CI)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)
Malignant tumor (SMQ)						
Placebo	177	325.21	10 (5.6)	3.07 (1.47, 5.65)		
Tafamidis Meglumine 20MG	88	174.03	6 (6.8)	3.45 (1.27, 7.50)	0.37 (-2.98,3.73)	1.12 (0.41, 3.08)
Tafamidis Meglumine 80MG	176	339.60	18 (10.2)	5.30 (3.14, 8.38)	2.23 (-0.88,5.33)	1.72 (0.80, 3.73)
Tafamidis 20 mg + 80 mg	264	513.63	24 (9.1)	4.67 (2.99, 6.95)	1.60 (-1.07,4.27)	1.52 (0.73, 3.18)

Reviewer's Comment: It is difficult to conclude a safety signal for malignancy based on small numbers of individual cases in the clinical studies. Skin cancers like basal cell carcinoma and squamous cell carcinoma are not uncommon in the disease patient population (i.e. older males). The carcinogenesis studies in animals indicate no

carcinogenic potential in two species: (1) in transgenic rasH2 mice treated with doses up to 90 mg/kg for 26 weeks and (2) In rats at exposure up to 18 times the AUC at the maximum recommended human dose for 2 years (see the non-clinical reviewer for details). Overall, the nonclinical and clinical evidence suggest that the risk of potential human carcinogenicity or tumor development related to tafamidis is probably unlikely.

8.7.2. Human Reproduction and Pregnancy

Based on findings from animal studies tafamidis may cause fetal harm when administered to a pregnant woman. Briefly, in animal reproductive studies, oral administration of tafamidis to pregnant rabbits during organogenesis resulted in adverse effects on development (embryofetal mortality, fetal body weight reduction and fetal malformation) and increased incidence of fetal skeletal variation.

Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis during gestation and lactation (see details in the preclinical review)

The Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) programs was implemented in April 2011 to monitor the progress and outcome of reported pregnancies in women directly and indirectly (through their partner) exposed to tafamidis. As of June 2018, there is limited human data (n=22) with tafamidis use (at a dose of 20 mg per day) during or within 1 month prior to pregnancy in the overall tafamidis program including post-marketing experience. The pregnancy outcomes of these 22 cases (includes 24 fetus) are listed as follows: 14 normal newborns-1 low birth weight and 2 pre-term infants, 5 unknown outcomes, 2 spontaneous abortions, 1 medical termination (Twins) and 1 voluntary abortion. Of the 14 normal newborns, there are no congenital abnormalities or impaired development (7 infants had post-natal follow-up at 1 year).

Tafamidis has been shown to be secreted in the milk of lactating rats. There are no available data on the presence of tafamidis in human milk, the effect on the breastfed infant, or the effect on milk production.

Reviewer's Comment: DCRP has consulted the Division of Pediatric and Maternal Health (DPMH) regarding how to manage the potential risk of reproductive and developmental toxicity through labeling and/or other regulatory measures. Based on findings from animal studies, pregnant women should be advised on the potential risk for a fetus and breastfeeding is not recommended during treatment with tafamidis. DCRP and DPMH also agree that collecting and establishing additional data from a world -wide, prospective, (b) (4) *observational study is necessary to assess the risks of pregnancy complications and adverse effects on the developing feus and neonate.*

8.7.3. Pediatrics and Assessment of Effects on Growth

Orphan drug designation (OD# 12-3633) for tafamidis for the treatment of ATTR amyloidosis in adult patients with cardiomyopathy was granted on 17 February 2012. In accordance with 21 CFR 314.55 (d), the applicant is exempted from the requirement of conducting a pediatric program.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The highest dose of tafamidis given to healthy human subjects was 480 mg in a single dose. There was one reported treatment-related AE of mild hordeolum at this dose level. There are two patients in the ATTR-CM phase 3 study experienced an acute accidental overdose of a single dose of 160 mg without the occurrence of any AE. Based on the clinical experiences, the risk for inadvertent or intentional overdose in humans in considered to be low.
There is no evidence that tafamidis has dependence potential based on the pharmacology and receptor binding. There is also no evidence suggesting effects of withdrawal and rebound of tafamidis. No adverse effects were reported in subjects who abruptly terminated treatment with tafamidis (e.g. subjects who went to liver transplant were required to discontinue treatment with tafamidis prior to transplant). This medication is intended for chronic use.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Tafamidis has not yet been approved for the treatment of ATTR-CM in any country to date.

Tafamidis was first approved on 16 November 2011 in the European Union (EU) for the treatment of TTR in adult patients with ATTR-PN. Since then, tafamidis 20 mg has been approved for the treatment of ATTR-PN in 41 countries. There have been approximately 4,783 patient-years of exposure to tafamidis from post-marketing experience as of 15 June 2018. In addition, an international, non-interventional study (THAOS) collects long-term, observational data on disease progression in patient with ATTR amyloidosis (with phenotypes ranging from ATTR-CM to ATTR-PN). As of 15 Feb 2018, there are a total of 785 patients with exposure to at least 1 dose of tafamidis in THAOS.

The applicant has identified several AESIs based on ongoing pharmacovigilance activities and inquiries including cardiac arrhythmia, central nervous system neoplasia, fall/dizziness/orthostatic hypotension, infection-related event and pancreatitis. The frequency of these AESIs has been evaluated in the phase 3 study in patients with ATTR-CM and other ATTR-CM studies. Overall, the incidence of these events of interest was similar compared to the

placebo group (see section 8.4.4).

Hepatotoxicity was also assessed in on-going ATTR-PN clinical studies and THAOS. There are a number of potential hepatic events. Majority of cases were related to a single or sporadic occurrence of increased hepatic enzyme/mild hepatoxicity after long period of therapy (i.e., ~1 year or longer) in which the events were resolved with or without temporary discontinuation of the therapy; few cases represent a negative re-challenge after tafamidis was restarted. There is one SAE of toxic hepatitis in THAOS thought to be related to tafamidis based on temporal relationship and a positive re-challenge. A brief summary of this event is listed below.

Patient (b) (6) A 49-year-old female subject in Portugal received tafamidis meglumine 20 mg once a day from (b) (6) for the treatment of transthyretin familial amyloid polyneuropathy (ATTR-PN). Medical history included anemia, hernia repair, and hiatus hernia. Approximately 7 weeks after starting tafamidis, the following laboratory findings were observed: ALT 450 IU/L (reference range 10-49), AST 832 IU/L (reference range 0-34),), alkaline phosphatase 219 IU/L (reference range 45-129), GGT 179 IU/L (reference range <38), total bilirubin 0.35 mg/dL (reference range <1). These laboratory findings occurred when the patient was hospitalized for an ECG abnormality. There was evidence of recovery prior to stopping tafamidis as significant reductions in ALT and AST serum levels were found on the same day that tafamidis therapy was withdrawn. On the day that tafamidis was stopped (which was 3 days after the liver function laboratory abnormalities were observed), ALT had decreased to 166 IU/L and AST to 50 IU/L. On 05 Feb 2013, an abdominal ultrasound revealed slightly increased liver dimensions with regular contours and coarse echo-structure, with no evidence of focal lesions in the analyzed segments. There was dilatation of the common bile duct up to 9.5 mm in diameter. The subject was discharged from the hospital on (b) (6) and recovered from the event of hepatitis on (b) (6) Tafamidis meglumine was restarted on (b) (6) after normalization of ALT and AST. However, on (b) (6) there was a very slight elevation in the level of transaminases (ALT 40 IU/L; AST 66 IU/L; GGT 44 IU/L), and tafamidis meglumine was permanently discontinued by the subject's own initiative on the same date. All serologies for infectious hepatitis completed on (b) (6) were negative. An analytical re-evaluation on (b) (6) (b) (6) confirmed complete normalization of liver function tests, and it was decided to permanently withdraw treatment with tafamidis meglumine as a result of the event of hepatitis. In the absence of other causes, the investigator considered the event to be a toxic hepatitis. In the opinion of the Investigator, the event of hepatitis was possibly related to tafamidis meglumine or a concomitant medication; the study Sponsor concurred with this assessment.

Reviewer's Comment: This hepatic event was thought to be related to tafamidis based on temporal relationship and a positive re-challenge. However, the marked elevations of ALT/AST in the incidence event (asymptotic) were accompanied by elevated ALP/GGT and normal BILI and ALT/AST had decreased significantly despite continuation of therapy for 3 days after the incident event. The observed liver abnormalities related to other

unknown cause cannot be ruled out. Though slightly elevated transaminases were observed after restarting of tafamidis, many drugs that could cause transient rises in serum transaminases do not cause progressive or severe drug-induced liver injury. Based on totality of evidence thus far, hepatotoxicity remains as a potential risk for tafamidis.

There is no additional safety signal identified through postmarket experience.

8.8.2. Expectations on Safety in the Postmarket Setting

The safety profile of tafamidis in patients with ATTR-CM is relatively benign. Tafamidis 80 mg is associated with a notable decrease in total thyroxine level and a numerically higher incidence of elevated ALT/AST compared to placebo; however, no corresponding clinical finings for thyroxine dysfunction and hepatoxicity were noted. Potential events relevant to thyroxine dysfunction and hepatoxicity in the post-marketing setting should be tracked and evaluated.

With limited human data up to date, the potential risk of reproductive and developmental toxicity in human remains unknown. Although the proportion of women of child bearing potential among ATTR-CM patients is expected to be small, there may be some pre-menopausal women with ATTR-PN. Accordingly, it is important to collect long-term safety data to monitor the pregnancy outcomes of women exposed to tafamidis and understand the demographic distribution (e.g. age) of these female patients in the post-marketing setting.

8.8.3. Additional Safety Issues From Other Disciplines

Clinical Pharmacology

An in vitro drug-transporter inhibition study (XT128402) demonstrated that tafamidis has the potential to inhibit Breast Cancer Resistance Protein (BCRP) both systemically and in the gastro-intestinal (GI) tract and may increase the exposure of BCRP substrates. A clinical study has not been conducted to date to characterize this interaction in vivo. A post marketing requirement (PMR) of a clinical drug interaction study is being issued, which will allow to evaluate the clinical significance of this interaction, inform the drug product label and to guide potential risk management strategies if a clinically significant interaction is observed in vivo.

8.9. Integrated Assessment of Safety

The clinical safety of tafamidis in patients with ATTR-CM was evaluated primarily using the controlled safety data from the 30-month phase 3 study. The safety dataset contains a total of 441 subjects who received at least one dose of study drug (n = 88, 176 and 177 in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively). The frequency of AEs/SAEs in

patients treated with tafamidis 20 mg or 80 mg was similar to that of placebo. Both doses of tafamidis were well tolerated in the study; there were only 2 subjects in the tafamidis 80 mg arm who required dose reductions due to an AE. In general, the safety profile for the low and high doses of tafamidis is similar.

A number of safety topics of interest have identified by the applicant and were evaluated in the phase 3 study. The topics are listed below:

- Identified risk from ATTR-PN studies: diarrhea, upper abdominal pain, UTI and vaginal infection
- Important potential risk from ATTR-PN studies: hypersensitivity, hepatotoxicity and thyroid dysfunction
- Signals identified from post-marketing: cardiac arrhythmia, central nervous system neoplasia, fall, dizziness, orthostatic hypotension, infection-related events and pancreatitis

Overall, there is no evidence suggesting any of these safety topics of interest are associated with tafamidis in patients with ATTR-CM. This benign safety profile of tafamidis is also supported by uncontrolled safety data in ATTR-CM patients. Few safety signals were identified by the reviewer and required for further assessment. Ocular AEs including cataract development were assessed by DTOP and it is believed that these events were likely not drug-related based on the background rate of cataract in the patient population. Although there was no imbalance in fall-related AEs in the phase 3 study, higher incidence of fall SAEs was found in the tafamidis groups compared to the placebo group (11.4% vs. 5.1%). Considering the background rate of fall in elderly, no clear mechanisms (e.g. no signal for hypotension or postural hypotension), as well as no signal found in the ATTR-PN program, the totality of data to date is limited to conclude the association between tafamidis and fall. Nevertheless, falls in this patient population could result in devastating outcomes and should be considered as a potential risk and tracked in the post-marketing setting.

Tafamidis is associated with a decrease in serum concentrations of total thyroxine without an accompanying change in TSH. A higher percentage of subjects in the tafamidis groups had total thyroxine < 0.8 x LLN compared to the placebo group [14%, 33% and 7% from the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively]. No corresponding clinical findings consistent with thyroid dysfunction have been observed. Given that there are minimal changes in TSH and lack of clinical evidence of thyroid dysfunction, normal thyroid function was probably maintained in subjects treated with tafamidis.

Elevated transaminases were observed rarely but more frequently in the tafamidis 80 mg group compared to the placebo group. There were 4 subjects (2%) and 5 subjects (3%) who had ALT ≥

3x ULN and AST ≥ 3x ULN, respectively in the tafamidis 80 group compared to 1 subject (<1%) and 0 subject in the placebo group. There were also two potential Hy's law cases based on combined liver function test abnormalities occurred at any time (ALT or AST ≥ 3 ULN and TB ≥ 2 ULN). Further review of these cases did no raise a major safety concern. The elevated liver function tests in these cases were likely secondary to patient's cardiac diseases and medical conditions. AE data also did not support the risk of hepatotoxicity in patients with ATTR-CM.

Since tafamidis (at a dose of 20 mg daily) received first regulatory approval in the EU in 2001 for the treatment of ATTR-PN, there is a cumulative post-marketing experience with more than 4,700 patient-years of exposure to tafamidis. Long-term safety data are also being collected in a non-interventional, observational study in patients with TTR amyloidosis globally (study THAOS, n =785 with a mean duration of exposure of 3.1 years). Overall, these data demonstrate a consistent safety profile of tafamidis.

Tafamidis is associated with a potential risk of reproductive and developmental toxicity based on animal data. There is limited human data with tafamidis exposure during pregnancy and the risk remains unknow. Pregnant women should be advised on the potential risk for a fetus and breastfeeding is not recommended during treatment with tafamidis.

Overall, Tafamidis has a largely benign and acceptable safety profile in patients with ATTR-CM. There are no safety issues that would preclude the approval of tafamidis. The potential risk of tafamidis can be managed through proper labeling and proposed pharmacovigilance activities outlined below:

Safety Concern	**Proposed pharmacovigilance activities**
Important potential risks	
Reproductive and developmental toxicity	Postmarketing requirements: Establish a (b) (4) observational study in women exposed to tafamidis during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate. DCRP and DPMH are working together to finalize the logistics of the requirement.

Hepatoxicity	DCRP and OSE will work together to evaluate potential hepatic events in the post-marketing setting
Thyroid dysfunction/hypothyroidism	DCRP and OSE will work together to evaluate potential events associated with thyroid dysfunction in the post-marketing setting
Fall	DCRP and OSE will work together to evaluate fall-related events in the post-marketing setting

9. Advisory Committee Meeting and Other External Consultations

None.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

We have provided our first round labeling edits to the applicant on March 11, 2019. The applicant responded to our labeling comments on March 20. 2019 (see the draft labeling). In general, the applicant is aligned with most of FDA's recommendations.

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no safety issues that warrant consideration of a REMS.

12. Postmarketing Requirements and Commitments

FDA will issue a PMR for the applicant to establish a worldwide, (b) (4) study in women exposed to tafamidis meglumine during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate. (b) (4) The study will collect information for a minimum of 10 years. (b) (4)

13. Appendices

13.1. References

See footnotes in text.

13.2. Financial Disclosures

Covered Clinical Study (Name and/or Number): Study B3461028

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 242		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 13 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study B3461045

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 158		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: Not applicable: N=0	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

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