CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211996Orig1s000 212161Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	211996	212161
SDN	5	1
Brand Name	VYNDAQEL	VYNDAMAX
Generic Name	Tafamidis meglumine	Tafamidis free acid
Dosage form and Strength	Capsule, 20 mg	Capsule, 61 mg
Submission Type	NME 505(b)(1) Priority review	NME 505(b)(1) Standard review
Link to EDR	\\cdsesub1\evsprod\NDA211996	\\cdsesub1\evsprod\NDA212161
Proposed dose	Tafamidis meglumine 80 mg (4 x 20 mg capsules), once daily. (b) (4)	Tafamidis free acid 61 mg, once daily. (b) (4)
Route of Administration	Oral	
Proposed Indication	Treatment of patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)	
Applicant	FoldRx Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.	
Submission Date	November 2, 2018	
Associated IND	IND 071880	
OCP Review Team	Snehal Samant PhD, Ruojing Li PhD, Chao Liu PhD, Sudharshan Hariharan PhD	
OCP Final Signatory	Mehul Mehta PhD Division Director Division of Clinical Pharmacology I	

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1. EXECUTIVE SUMMARY

This Clinical Pharmacology review is for an original NME NDA for VYNDAQEL (tafamidis meglumine 20 mg capsule) submitted by FoldRx to the Division of Cardiovascular and Renal products (DCaRP) under section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-CM is a rare and fatal disorder associated with destabilization of native TTR tetramer resulting in progressive amyloid deposition in the myocardial tissue. Currently there are no approved drugs in the United States (US) and worldwide for the treatment of ATTR-CM. Tafamidis binds to TTR tetramer and stabilizes it against dissociation to monomers, the rate limiting step in the formation of TTR amyloid. The Applicant is seeking approval for VYNDAQEL 80 mg once daily dose (4 x 20 mg tafamidis meglumine capsules) to reduce all-cause mortality and frequency of cardiovascular-related hospitalization in patients with wild type or hereditary ATTR-CM.

The Applicant is primarily relying on the efficacy and safety information from the pivotal placebo-controlled Phase 3 trial (B3461028) evaluating two once daily dosing regimens of tafamidis meglumine, 20 mg and 80 mg, in ATTR-CM patients. The Phase 3 trial met its primary endpoint as well as key secondary endpoints for the pooled tafamidis compared to placebo. A long-term, double-blind, extension study (B3461045) of the Phase 3 trial is currently on-going.

The Applicant is also seeking approval of VYNDAMAX (tafamidis free acid 61 mg capsule) under NDA 212161 for the treatment of ATTR-CM. (b) (4) the Applicant developed tafamidis free acid 61 mg capsule to provide a single capsule equivalent to the proposed 80 mg dose of tafamidis meglumine. Two relative bioavailability studies to demonstrate a pharmacokinetic (PK) bridge for tafamidis free acid 61 mg capsule to tafamidis meglumine 4 x 20 mg capsules were submitted to the Clinical Pharmacology module of NDA 211996. Additionally, five Phase 1 studies supporting initial development of tafamidis free acid formulation, one single ascending dose study, one QT study, one Phase 1 study to evaluate effect of race/ethnicity on tafamidis PK and three population PK/PD analysis reports were submitted to the Clinical Pharmacology module of NDA 211996.

The Applicant had submitted an original NDA (202737) for tafamidis meglumine 20 mg to the Division of Neurology Products (DNP) in December 2011 for the ATTR-polyneuropathy (ATTR-PN) indication. A Complete Response (CR) letter was issued on June 15, 2012 (b) (4)

Clinical pharmacology of tafamidis previously reviewed under NDA 202737 is summarized in this review.

The key issues addressed in this clinical pharmacology review are:

1) The appropriateness of the proposed tafamidis meglumine 80 mg once daily dose for the treatment of ATTR-CM.
2) Appropriateness of the proposed dosing for ATTR-CM patients with hepatic impairment.
3) Assessment of the drug interaction potential of tafamidis with major drug metabolizing enzymes and transporters.
4) Assessment of the relative bioavailability of Phase 3 clinical trial formulation to the to-be-marketed formulation of tafamidis meglumine 80 mg.
5) Assessment of the relative bioavailability of tafamidis free acid 61 mg oral capsule to tafamidis meglumine 80 mg.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted to NDA211996 and NDA212161 and finds it adequate to support approval of VYNDAQEL and VYNDAMAX for the proposed indication in ATTR-CM patients.

Review Summary	Acceptable to OCP	Comments
Pivotal or supportive evidence of effectiveness	☑Yes ☐No ☐N/A	Pivotal evidence of effectiveness in reduction of all-cause mortality and frequency of cardiovascular related hospitalizations as demonstrated in the Phase 3 trial in ATTR-CM patients.
General dosing instructions	☑Yes ☐No ☐N/A	VYNDAQEL: The recommended dosage is 80 mg (four 20 mg tafamidis meglumine capsules) orally once daily. (b) (4). VYNDAMAX: The recommended dosage is 61 mg (one 61 mg tafamidis free acid capsules) orally once daily. (b) (4).
Dosing in patient subgroups (intrinsic and extrinsic factors)	☑Yes ☐No ☐N/A	No dose adjustment is needed in patients based on age, body weight, gender, race/ethnicity and renal function. No dose adjustment is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on tafamidis PK is not known.
Labeling	☑Yes ☐No ☐N/A	Pending agreement with the Applicant
Bridge between the to-be-marketed and	☑Yes ☐No ☐N/A	To-be marketed tafamidis meglumine 20 mg oral capsule formulation manufactured by Catalent is bioequivalent to the Phase 3 clinical trial formulation manufactured by (b) (4)

clinical trial formulations		No clinically significant differences in steady state peak plasma concentration (C_{max}) and area under the plasma concentration over time curve (AUC) of tafamidis were observed for Tafamidis 61 mg capsule compared to tafamidis meglumine administered as four 20 mg capsules. Findings from inspection of the clinical site are pending at the time of finalizing this review. No issues were identified at the analytical site following inspection.

1.2 Post-Marketing Requirements and Commitments

In vitro drug-transporter inhibition study (XT128402) demonstrates that tafamidis has the potential to inhibit Breast Cancer Resistance Protein (BCRP) 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) to conduct a clinical study to assess the clinical drug interaction potential of tafamidis with a relevant BCRP substrate will be sent to the Applicant. Pending results from this study, the potential risk for drug interaction with BCRP substrates and need for dose adjustment has been addressed in labeling.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

TTR is a transport protein for thyroxine (T_4) and retinol/retinol-binding protein complex. TTR is secreted by the liver as a homotetramer. Tafamidis binds to the two thyroxine (T_4) binding sites of TTR (dissociation constants for the first binding site (K_{d1B}) of 2 to 3 nM, and dissociation constants for the second binding site (K_{d2B}) of 154 to 278 nM), and in doing so, it stabilizes the TTR tetramer against dissociation to TTR monomers, the rate limiting step in the formation of TTR amyloid.

(b) (4). ATTR-CM can be inherited as an autosomal dominant trait caused by mutation in the TTR gene, or by deposition of wild-type transthyretin protein. Tafamidis stabilized both the wild type TTR tetramer and the tetramers of 14 TTR variants tested clinically following a once-daily dosing regimen. Tafamidis also stabilized the TTR tetramer for 25 variants tested ex vivo.

Absorption

Median tafamidis peak concentrations were attained within 4 hours following once daily dose of VYNDAQEL. Tafamidis exposure increases proportionally over single (up to 480 mg) or multiple (up to 80 mg) once daily dosing. The apparent clearance was similar after single and repeated administration of tafamidis meglumine 80 mg.

Effect of food

No clinically significant difference in the pharmacokinetics of tafamidis was observed following administration of a high fat, high calorie meal.

Distribution

The apparent steady-state volume of distribution of tafamidis is approximately 16 liters. Plasma protein binding of tafamidis is >99%, in vitro. Tafamidis primarily binds to TTR tetramer.

Elimination

The mean terminal elimination half-life of tafamidis is approximately 49 hours. Accumulation occurred with once daily dosing, with mean accumulation ratio values ranging from 2.1 to 2.7. The apparent oral clearance of tafamidis is 0.228 L/h. The metabolism of tafamidis has not been fully characterized. However, glucuronidation has been observed. After single oral dose of tafamidis meglumine 20 mg, approximately 59% of the dose was recovered in feces (mostly unchanged drug) and approximately 22% of the dose was recovered in urine (mostly as the glucuronide metabolite). Phase II enzymes uridine 5'- diphospho- glucuronosyltransferase (UGT) 1A9, UGT1A1, and UGT1A3 appear to be the major isoforms responsible for the formation of the acyl glucuronide, while minor activity was observed with UGT isoforms 1A6, 1A7, 1A8, and 2B7.

Intrinsic factors

No clinically significant difference in the pharmacokinetics of tafamidis was observed with age (18-88 years), race/ethnicity (Caucasian and Japanese) or renal impairment. No dose-adjustment is required for these factors.

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

Drug-drug interactions

Clinical Studies

No clinically significant difference in the pharmacokinetics of midazolam (a CYP3A4 substrate) or on the formation of its active metabolite (1 hydroxymidazolam) was observed when a single 7.5 mg dose of midazolam was administered prior to and after a 14-day regimen of tafamidis meglumine 20 mg once daily.

In Vitro Studies

Cytochrome P450 Enzymes: Tafamidis induces CYP2B6 and CYP3A4 and does not induce CYP1A2. However, static-mechanistic model predictions show that the potential of tafamidis meglumine 80 mg once daily to induce CYP3A4 or CYP2B6 is low. Tafamidis does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 or CYP2D6.

UGT: Tafamidis inhibits UGT1A1. However, it does not induce or inhibit other UGT substrates.

Transporter Systems: Tafamidis inhibits BCRP and organic anion transporters OAT1 and OAT3. Tafamidis did not show a potential to inhibit P-glycoprotein (P-gp), organic cation transporter OCT2, organic anion transporting polypeptide OATP1B1 and, OATP1B3, and multidrug and toxin extrusion transporters MATE1, and MATE2K at clinically relevant concentrations.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosage is 80 mg tafamidis meglumine (four 20 mg tafamidis meglumine capsules) orally once daily. (b) (4).

2.2.2 Therapeutic individualization

No dose adjustment is needed in patients based on age, body weight, gender, race/ethnicity and renal function. No dose adjustment is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on tafamidis is not known.

2.3 Outstanding Issues

NA

2.4 Summary of Labeling Recommendations

The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

Labeling recommendation was made to add a sub-section to Section 7 Drug Interactions to describe the potential for a drug-drug interaction of tafamidis with BCRP substrates.

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

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Physicochemical attributes of the drug product

Tafamidis meglumine is the meglumine salt form of 2-(3, 5-dichloro-phenyl)-benzoxazole-6-carboxylic acid, or tafamidis free acid. Tafamidis meglumine is supplied as a 20 mg soft gelatin capsule containing a white to pink colored suspension of tafamidis meglumine 20 mg (equivalent to 12.2 mg of tafamidis free acid) for oral use. The inactive ingredients include: ammonium hydroxide 28%, brilliant blue FCF, carmine, ethyl alcohol, gelatin, glycerin, iron oxide (yellow), isopropyl alcohol, polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitan monooleate, sorbitol, and titanium dioxide.

The Applicant has developed a tafamidis free acid 61mg soft gelatin capsule containing a white to pink colored suspension of tafamidis 61 mg and the following inactive ingredients: ammonium hydroxide 28%, butylated hydroxytoluene, ethyl alcohol, gelatin, glycerin, iron oxide (red), isopropyl alcohol, polyethylene glycol 400, polysorbate 20, povidone (K-value 90), polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol, and titanium dioxide.

Regulatory Background

Development of tafamidis meglumine for ATTR-CM was under IND 071880, submitted on August 19, 2005. Orphan Drug Designation (ODD) #12-3633 was granted for tafamidis for the treatment of symptomatic transthyretin amyloid cardiomyopathy on February 17, 2012. The clinical development program was granted Fast Track designation on May 17, 2017 and, Breakthrough Therapy designation (BTD) was granted on May 18, 2018 for the treatment of transthyretin amyloidosis in adult patients with cardiomyopathy (due to wild type or variant TTR) to reduce the combination of all-cause mortality and cardiovascular hospitalization.

The applicant had originally submitted NDA (202737) to the DNP in December 2011 for tafamidis meglumine, 20 mg oral capsules for the indication of treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy (ATTR-PN) to delay neurologic impairment (IND 074866). The Sponsor received a Complete Response Letter for NDA 202737

dated June 15, 2012 [redacted] (b) (4)

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Tafamidis is a selective stabilizer of both tetrameric wild-type (WT) and amyloidogenic variants of TTR tetramer. Tafamidis binds to the two thyroxine binding sites of TTR tetramer and inhibits its dissociation to TTR monomers. This inhibits subsequent formation of amyloid from misfolded TTR monomers and is expected to limit deposition of amyloid in the cardiac tissues.
Cardiac Electrophysiology	No inhibition of the hERG potassium channel current in transfected human kidney embryo 293 cells was observed at tafamidis concentrations of 1, 3, 10 and 30 µM. A supra-therapeutic single 400 mg oral-dose of tafamidis meglumine solution did not prolong the QTc interval to any clinically relevant extent as evaluated in a randomized, placebo- and positive-controlled, cross-over TQT study in healthy adults. The supratherapeutic C_{max} was approximately 2. 2-fold higher than the steady state C_{max} following tafamidis meglumine 80 mg dose.
General Information	
Bioanalysis	Tafamidis plasma concentrations were measured by a validated liquid chromatography- tandem mass spectrometry assay (Refer Appendix 4.1)
Healthy adults vs patients	Tafamidis PK is similar between healthy adults and ATTR-CM patients
Dose proportionality	Tafamidis PK is dose-proportional over single (up to 480 mg) or multiple (up to 80 mg) once daily dosing.
Variability	Intra-subject variability for tafamidis C_{max} and $AUC_{0\text{-last}}$ ranges from 11% to 24%
Absorption	
T_{max}	Median tafamidis peak concentrations occurred within 4 hours following dosing.
Accumulation	Accumulation occurred with once daily dosing, with mean accumulation ratio values ranging from 2.1 to 2.7

Food effect	No clinically significant differences in the pharmacokinetics of tafamidis were observed following administration of a high fat, high calorie meal.
Distribution	
Volume of distribution	The apparent steady-state volume of distribution of tafamidis is approximately 16 liters.
Protein binding	Plasma protein binding of tafamidis to human serum albumin is >99.6 % in vitro.
Substrate of transporter systems	Tafamidis is not a substrate of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and MATE1, MATE2K
Elimination	
Half-life	The mean terminal elimination half-life of tafamidis is approximately 49 hours. The apparent oral clearance of tafamidis meglumine is 0.228 L/h.
Metabolism	
Metabolizing enzymes	The Phase II conjugating enzymes UGT 1A9, UGT 1A1, and UGT 1A3 appear to be the major isoforms responsible for the formation of the acyl glucuronide, while minor activity was observed with UGT isoforms 1A6, 1A7, 1A8, and 2B7.
Excretion	
Primary excretion pathways	After a single oral dose of tafamidis meglumine 20 mg, approximately 59% of the dose was recovered in feces (mostly unchanged drug) and approximately 22% of the dose was recovered in urine (mostly as the glucuronide metabolite).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical Outcomes

The pivotal evidence of effectiveness for tafamidis to reduce all-cause mortality and frequency of cardiovascular related hospitalization in patients with wild type or hereditary ATTR-CM is demonstrated by the randomized, double-blind, placebo-controlled, multi-center, Phase 3 trial (B3461028) evaluating the efficacy and safety of tafamidis meglumine 20 mg and 80 mg doses in ATTR-CM patients. A total of 441 patients diagnosed with ATTR-CM were randomized 2:1:2 to the three arms: placebo, tafamidis meglumine 20 mg, and tafamidis meglumine 80 mg for a treatment duration of 30 months. Randomization was stratified by TTR wild or hereditary genotype and NYHA disease severity classification at baseline.

Phase 3 trial met its primary efficacy end-point of a statistically significant reduction in the combined all-cause mortality and frequency of cardiovascular-related hospitalizations (using a hierarchical combination, applying the method of Finkelstein-Schoenfeld) for pooled tafamidis meglumine 20 mg and 80 mg arms compared to placebo at Month 30 (**Table 1**). The Phase 3 trial also met its key secondary endpoints of a statistically significant change from Baseline to Month 30 in the distance walked during the six- minute walk test (6MWT) (LS mean difference from placebo 75.7 m (95% CI 57.6, 93.8)), and in the Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) score ((LS mean difference from placebo 13.7 (95% CI 9.5, 17.8) for pooled tafamidis compared to placebo. The significant difference in the key secondary endpoints between pooled tafamidis and placebo was first observed at Month 6 and remained significant through Month 30. The other secondary endpoints were cardiovascular-related mortality, frequency of cardiovascular-related hospitalization, all-cause mortality and TTR stabilization at Month 1 (measured by the ex-vivo TTR stabilization assay). Please refer to Clinical review by Drs. Preston and McDowell for results pertaining to these secondary endpoints.

TTR Stabilization

The TTR stabilization, was measured by the ex-vivo TTR stabilization assay at baseline and Months 1, 6, 12, 18, 24, and 30 (or early study discontinuation) of the treatment duration of the Phase 3 trial. Refer to Appendix 4.2 for description of the TTR tetramer assay and calculation of %TTR tetramer stabilization values. The Applicant conducted a population PK-PD analysis using data from 11 clinical studies submitted to NDA 211996 to characterize the relationship between the molar ratio of tafamidis:TTR tetramer and TTR tetramer stabilization (Please see Appendix 4.3 for further details). The relationship between percentage stabilization of TTR tetramer and the molar ratio of tafamidis:TTR tetramer was adequately described by a sigmoid Emax model. Healthy volunteers demonstrated the largest maximum percentage TTR tetramer stabilization (354%), followed by patients with ATTR-PN (279%), then patients with ATTR-CM (236%). The EC_{50} in healthy volunteers was estimated higher (2.2) compared to patients with ATTR-CM and ATTR-PN (0.897).

NT-proBNP

Change from baseline in cardiac biomarker, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentration, in the pooled tafamidis group was an exploratory endpoint in Study B3461028 and favored the pooled tafamidis group compared to placebo. The LS mean Month 30 change from baseline difference in NT-proBNP concentration from the placebo group was -2181 (pg/mL) (95% CI -3326.14, -1034.95) for the pooled tafamidis group.

Overall, a clinically relevant, statistically significant reduction in all-cause mortality and frequency of CV-related hospitalizations at Month 30 was demonstrated for ATTR-CM patients treated with tafamidis compared to those treated with placebo. There were also improvements in percent TTR stabilization and NT-proBNP with treatment compared to placebo.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of tafamidis meglumine 80 mg, once daily (QD) is acceptable for the treatment of patients with wild type or hereditary ATTR-CM. The Phase 3 ATTR-CM trial was not powered for statistical comparison of the primary endpoint of the individual tafamidis meglumine 20 mg and 80 mg doses to placebo. The exploratory sub-group analysis by dose demonstrated a similar and clinically meaningful treatment effect for both, 20 mg and 80 mg tafamidis doses compared to placebo (**Table 1**).

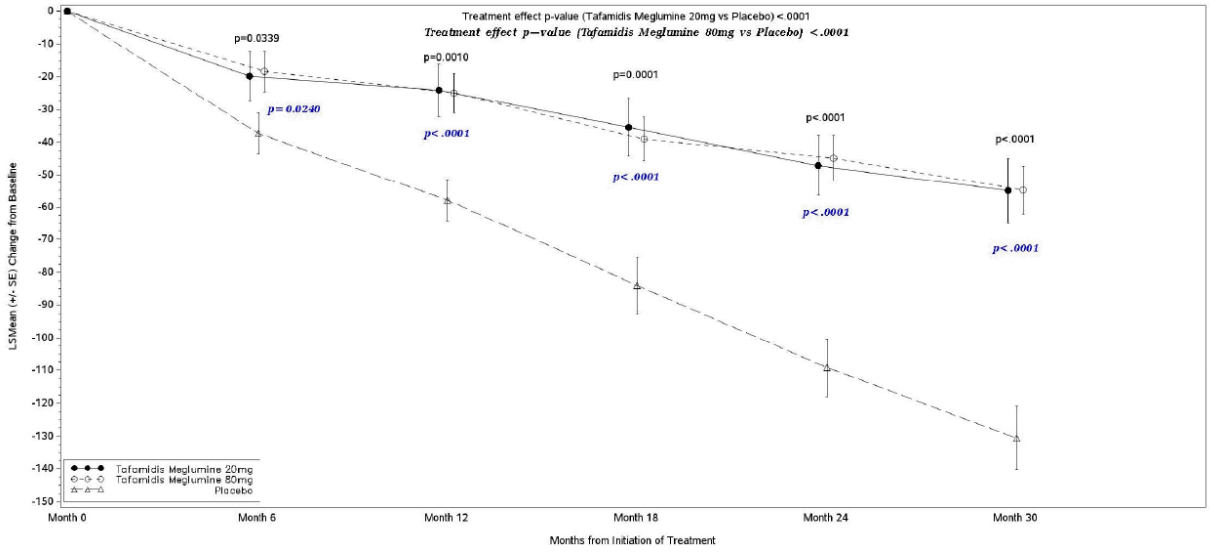
Table 1. Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of cardiovascular- related hospitalizations at Month 30

	Tafamidis meglumine 20 mg (n=88)	Tafamidis meglumine 80 mg (n=176)	Pooled Tafamidis (n=264)	Placebo (n=177)
Number of subjects alive, n (%)	64 (72.7)	122 (69.3)	186 (70.5)	101 (57.1)
Average frequency of CV-related hospitalizations during 30 months (per year) among those alive at Month 30	0.218	0.339	0.297	0.455
p-value from Finkelstein-Schoenfeld method	0.0048	0.003	0.0006	

Intent-to-treat (ITT) analysis set
Source: Table 16-CSR Study B3461028

Change from baseline in the distance walked during 6MWT for the ITT analysis set was similar for both, 20 mg (LS mean difference from placebo 75.7 m (95% CI of difference 48.7, 102.7))and 80 mg (LS mean difference from placebo 75.8 m (95% CI 55.9, 95.6)) tafamidis meglumine dose groups from the first observation at Month 6 up to the last observation at Month 30 (**Figure 1**).

Figure 1. Distance walked during 6-Minute Walk Test (6MWT) LS means (SE) change from baseline to Month 30 by dose



ITT analysis set
Source: Figure 12-CSR Study B3461028

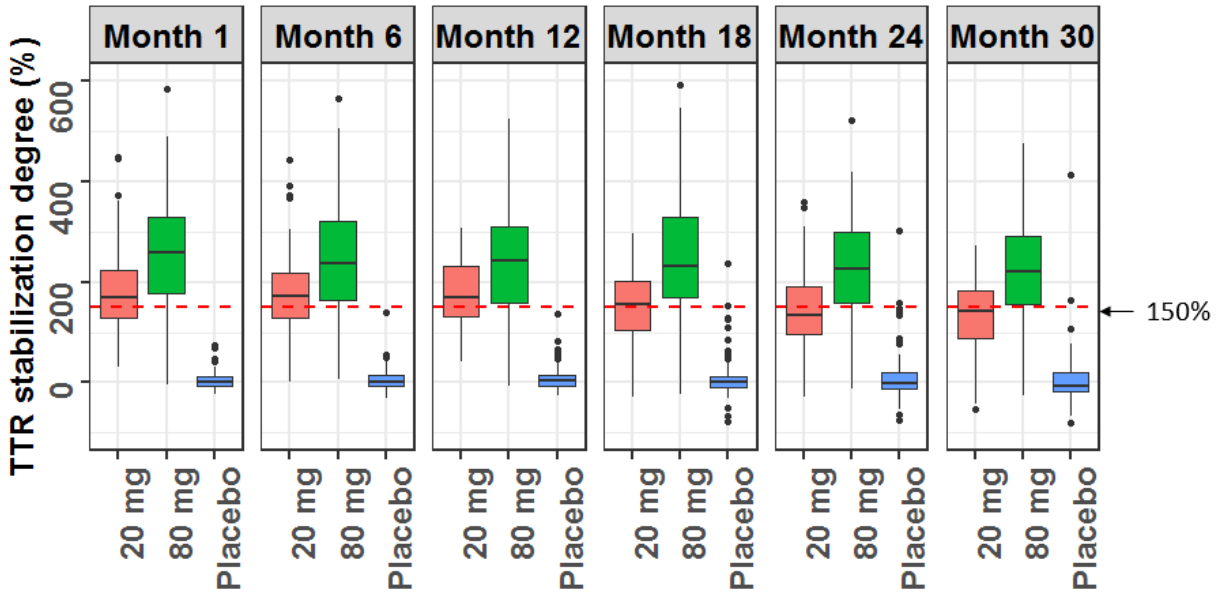
A statistically significant change from baseline in the KCCQ-OS score compared to placebo for the ITT analysis set was first observed at Month 6 and remained significant through Month 30 for the tafamidis meglumine 80 mg dose group. For the 20 mg tafamidis dose, a significant change from baseline in the KCCQ-OS score compared to placebo was first observed at Month 12 and remained significant through Month 30.

Overall, both the 80 mg and 20 mg tafamidis meglumine doses demonstrated similar efficacy in terms of the primary and secondary efficacy endpoints of the Phase 3 trial. In terms of safety, both tafamidis 20 mg and 80 mg dose groups were well tolerated and demonstrated comparable safety in the Phase 3 trial. The Phase 3 trial had provision for dose-reduction and only 2 patients (1.1%) in the tafamidis meglumine 80 mg group were down-titrated to 20 mg. Please refer to Clinical review by Drs. McDowell and Dunnmon for more information on the safety analysis of the Phase 3 trial. Therefore, based on the clinical outcome findings from the Phase 3 trial, the two doses i.e., 20 mg and 80 mg tafamidis meglumine, were similar in terms of efficacy and safety compared to placebo.

TTR stabilization
The review team conducted independent analysis to assess the degree of TTR tetramer stabilization for the three treatment groups – placebo, tafamidis meglumine 20 mg and 80 mg, from Months 1 to 30 in the ATTR-CM Phase 3 trial. Both, 20 mg and 80 mg tafamidis meglumine doses showed a higher degree of TTR stabilization (%) compared to placebo for the entire treatment duration of the Phase 3 trial (**Figure 2**). The mean TTR stabilization degree (%)

was relatively higher for the tafamidis meglumine 80 mg dose compared to tafamidis meglumine 20 mg dose from Month 1 to Month 30 (**Figure 2**), indicating that TTR stabilization results favored tafamidis meglumine 80 mg dose, which was consistent with Applicant's results from population PK/PD analysis for TTR stabilization (details refer to Appendix 4.3). The median percentage TTR stabilization estimated from the Applicant's population PK/PD model was greater in the tafamidis meglumine 80 mg treatment group (221%) compared to the 20 mg group (141%).

Figure 2. TTR stabilization degree stratified by dose from Month 1 through Month 30 of the Phase 3 trial B3461028



Source: Reviewer's analysis

Red box is 20 mg dose, green box is 80 mg dose, and blue box is placebo group. The red dash line is reference line indicating the TTR stabilization degree cut-off of 150%.

To differentiate the two doses further, the reviewer used arbitrary cut-off of 150% and compared the proportion of patients attaining the cut-off between the two tafamidis meglumine dose groups. At month 1, there were 0% (0/171) of patients in placebo, 55% (44/80) of patients in tafamidis 20 mg, and 75% (123/164) of patients in tafamidis 80 mg treatment groups that attained 150% TTR stabilization. At month 30, there were 2.5% (2/81) of patients in placebo, 40.4% (23/57) of patients in tafamidis 20 mg, and 72.3% (73/101) of patients in tafamidis 80 mg treatment groups that attained 150% TTR stabilization. Thus, correspondingly higher proportion of patients in the tafamidis meglumine 80 mg dose group attain greater TTR stabilization compared to tafamidis 20 mg dose group.

Tafamidis shows a dose-dependent increase in the degree of TTR stabilization. Although, there is no clear relationship between higher drug exposure and the clinical efficacy outcomes,

comparatively greater degree of TTR stabilization with the 80 mg tafamidis meglumine dose aligns with the mechanism of action of tafamidis which involves stabilizing the TTR tetramer against dissociation to TTR monomers. The comparable safety and efficacy profiles of the 20 mg and 80 mg tafamidis meglumine doses and relatively higher degree of TTR stabilization by tafamidis meglumine 80 mg provide adequate information in support of tafamidis meglumine 80 mg as the recommended dose for the treatment of patients with wild type or hereditary ATTR-CM.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen or management strategy is not required in patients based on age, body weight, gender, race.

Renal impairment

Following single and multiple oral dosing of tafamidis meglumine (15 to 60 mg), < 3.2% of the dose is excreted as unchanged tafamidis in the urine and ~6.8% to 10.8% is excreted as unchanged tafamidis + its glucuronide conjugate (Study Fx-002). Absolute bioavailability of tafamidis is not known. Following administration of single oral radiolabeled dose of tafamidis meglumine 20 mg, 58.5% (49%-65%) and 22.4% (13%-34%) of the total dose administered was recovered in feces and urine, respectively, with 80.9% mean total recovery of radioactivity collected up to 16 to 23 days. While metabolites were not definitively identified in the mass-balance study (Study Fx1a-107), glucuronidation has been observed. These data suggest hepatobiliary route to be the major route of elimination for tafamidis.

In addition, creatinine clearance was not found to be a significant covariate of tafamidis PK from the population PK model. Although a dedicated clinical study to characterize the effect of renal impairment on tafamidis PK has not been conducted, based on totality of evidence, renal elimination likely is a minor pathway contributing to elimination of unchanged tafamidis. Therefore, no dose adjustment is required for patients with renal impairment.

Hepatic impairment

The effect of hepatic impairment on PK of tafamidis was evaluated in mild (Child-Pugh score of 5-6) and moderate hepatic impairment subjects (Child-Pugh score of 7-9), (Study B3461016 (Fx1A-105)). The effect of severe hepatic impairment on tafamidis has not been evaluated. Following a single dose of tafamidis meglumine 20 mg, C_{max} was similar between healthy (1.28 (µg/mL) (24.9% CV)) and moderate hepatic impaired subjects (1.38 (µg/mL) (40.5% CV)). Tafamidis mean $AUC_{0\text{-}inf}$ was decreased by 42% in moderate hepatic impairment subjects (39.6 (µg.h/mL) (18.8% CV)) compared to healthy subjects (68.1 (µg.h/mL) (23.7% CV)). Moderately hepatic impaired subjects had lower albumin and TTR levels, which reduced the overall binding capacity in plasma resulting in higher apparent clearance of total tafamidis (0.52 L/h vs 0.31L/h).

TTR tetramer plasma levels are lower by ~50% in moderate hepatic impairment (24.3 mg/dL (18.5% CV) compared to healthy subjects (10.7 mg/dL (55.4% CV)). Although predicted steady state tafamidis trough plasma concentration decreases by 44% in moderate hepatic impairment subjects compared to healthy subjects, the relative levels of tafamidis and TTR tetramer concentration expressed as trough Tafamidis: TTR mean molar ratio, is similar between subjects with moderate hepatic impairment and healthy volunteers (**Table 2**).

There are no clinically significant differences in the tafamidis PK in mild hepatic impairment subjects compared to healthy subjects. Subjects with mild hepatic had similar levels of albumin and TTR as healthy subjects, with similar trough Tafamidis: TTR mean molar ratio (0.40 (0.06 SD) in healthy vs 0.41 (0.09 SD) in mild hepatic impairment). No dose adjustment is needed in patients with mild or moderate hepatic impairment.

Table 2. Trough Tafamidis: TTR mean molar ratio values by hepatic function

	Healthy (n=9)	**Moderately hepatic impaired (n=9)**
Arithmetic mean (SD)	0.44 (0.07)	1.10 (0.80)
Median	0.32	0.5
Range	0.43, 0.58	0.93, 3.12
CV%	0.20	0.70

Source: Table 26 - CSR B3461016

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug interaction

Administration with a high fat, high calorie meal does not have a clinically significant effect on the pharmacokinetics of tafamidis following administration of tafamidis meglumine 80 mg (4 x 20 mg tafamidis meglumine capsules). Administration of 61 mg tafamidis free acid capsule with a high-fat, high-calorie meal increases mean C_{max} of tafamidis by 32% without affecting AUC. Dose/exposure related adverse events have not been observed for tafamidis (Refer Clinical review by Dr. McDowell and Dr. Preston) in the ATTR-CM Phase 3 study. Given the absence of any exposure related adverse events, a 32% increase in C_{max} following administration of tafamidis free acid with food does not seem to be of clinical significance.

Drug-Drug interactions

1. Tafamidis inhibits BCRP in-vitro. The in-vitro study (XT128402 (12-02143)) of BCRP (ABCG2) inhibition by tafamidis in MDCKII-BCRP cells with prazosin as the BCRP probe substrate showed that tafamidis inhibits BCRP substrate uptake in a concentration dependent manner with an IC_{50} value of 1.16 µM. The in vitro study demonstrates that tafamidis has

the potential ($I_{gut}/IC_{50} \geq 10$) to inhibit BCRP and may increase exposure of BCRP substrates. A clinical study has not been conducted to date to characterize this interaction in vivo. A PMR is requested to conduct a clinical drug interaction study to evaluate the potential interaction between tafamidis and a relevant BCRP substrate. The recommended clinical drug interaction study 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. Pending a clinical DDI study the labeling is updated in Section 7. DRUG INTERACTIONS/7.1 BCRP substrates to communicate the potential risks and the need for dose adjustment of BCRP substrates.

2. OAT1, OAT3: The in-vitro study (XT-403-Pfizer-38-07 May 2012) demonstrates that tafamidis has a potential to inhibit the organic anion transporter, OAT3, at 80 mg tafamidis meglumine dose (IC_{50} = 2.36 μM, $C_{max, unbound}/IC_{50}$ = 0.12). The maximal increase in AUC of OAT3 substrates using static-mechanistic model was predicted to be 11 to 24%. Based on the in vitro study and model predictions, tafamidis has a low potential for clinically significant interaction with OAT3 substrates.
3. Based on the in vitro DDI studies, tafamidis did not show a potential to inhibit P-gp, OCT2, OATP1B1, OATP1B3, and MATE1, and MATE2K at clinically relevant concentrations.
4. In vitro studies with human liver microsomes do not demonstrate potential for tafamidis for inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2B6, and CYP3A4/5 (R_1 < 1.02).
5. In the presence of BSA, tafamidis demonstrated little or no reversible inhibition of UGT isozymes 1A1, 1A4, 1A6, 1A9 and 2B7 (IC_{50} > 100 μM). In the absence of 2% BSA, UGT 1A1, 1A4 and 2B7 activities were inhibited with IC50 values of 30, 86, and 83 μM, respectively.
6. Tafamidis did not cause induction of CYP1A2 in vitro. Tafamidis induced CYP3A4 in vitro with an EC_{50} of 28 μM. Similarly, tafamidis induced CYP2B6 in vitro with an EC_{50} of 25 μM. The in vitro studies demonstrate that tafamidis has a potential to induce CYP3A4 and CYP2B6 at the tafamidis free acid 61 mg dose (R_3 < 0.8). However, the maximal decrease in AUC of CYP3A4 and CYP2B6 substrates using static-mechanistic model was predicted to be only 9% and 15%, respectively, on administration of tafamidis free acid 61 mg. Additionally, clinical DDI study with midazolam, a probe CYP3A substrate, did not show any clinically significant impact on the PK of midazolam and its active metabolite when co-administered with tafamidis meglumine 20 mg once daily. Therefore, based on the totality of evidence, the potential for tafamidis to induce CYP3A4 or CYP2B6 is low following 80 mg tafamidis meglumine or 61 mg tafamidis free acid.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Change in manufacturing site of the drug product

The pivotal Phase 3 clinical study B3461028 initially utilized 20 mg tafamidis meglumine soft gelatin capsules manufactured by (b) (4) The manufacturing site was transferred to Catalent Pharma Solutions (Catalent). To support the change of manufacturing site and to demonstrate a PK bridge between the clinical trial formulation used initially and to-be-marketed formulation, Study B3461044 was conducted in healthy adults to evaluate the relative bioavailability of tafamidis meglumine 20 mg capsule manufactured by Catalent (Test) compared to tafamidis meglumine 20 mg capsule manufactured by (b) (4) (Reference) under fasting conditions. Following the completion of the relative bioavailability study, tafamidis meglumine 20 mg capsules manufactured by Catalent were provided to be administered in the Phase 3 clinical trial B3461028. The 90% CIs for the Test/Reference geometric mean C_{max} and $AUC_{0\text{-}inf}$ ratios are within the 80 – 125% bioequivalence range (**Table 3**). The mean $t_{1/2}$ (48.1 ± 10.9 h for Catalent vs 49.8 ± 11.6 h for (b) (4) and median T_{max} are similar (2.0 h (0.5-6.1 h) for Catalent vs 2.0 h (0.5-8.0 h) for (b) (4) for both the formulations. Between-subject variability of tafamidis PK was similar for both the formulations (18-24% CV). The relative bioavailability study was not of a replicate crossover design to evaluate the intra-subject variability.

Table 3. Statistical summary of PK parameters of relative bioavailability study of 20 mg Tafamidis Meglumine Capsule Manufactured by Catalent (Test) versus 20 mg Tafamidis Meglumine Capsule Manufactured by (b) (4) Study B3461044)

Parameter (Unit)	Adjusted geometric mean		Ratio (T/R) of the geometric mean (%)	90% C.I of the ratios
	Test (T)	Reference (R)		
C_{max} *(µg/mL)*	1.21	1.21	100.5	(94.8, 106.4)
$AUC_{0\text{-}t}$ *(µg.hr/mL)*	58.3	58.9	99.1	(95.3, 103.0)
$AUC_{0\text{-}\infty}$ *(µg.hr/mL)*	62.3	63.5	98.2	(93.7, 102.9)

Source: Table 11 CSR B3461044

Tafamidis free acid capsule formulation

Tafamidis meglumine 80 mg dose was administered as 4 x 20 mg tafamidis meglumine capsules in the Phase 3 trial (b) (4) . The Applicant developed tafamidis free acid 61 mg capsule formulation to provide a single capsule to achieve the recommended daily dose equivalent to tafamidis meglumine 80 mg, to limit pill burden.

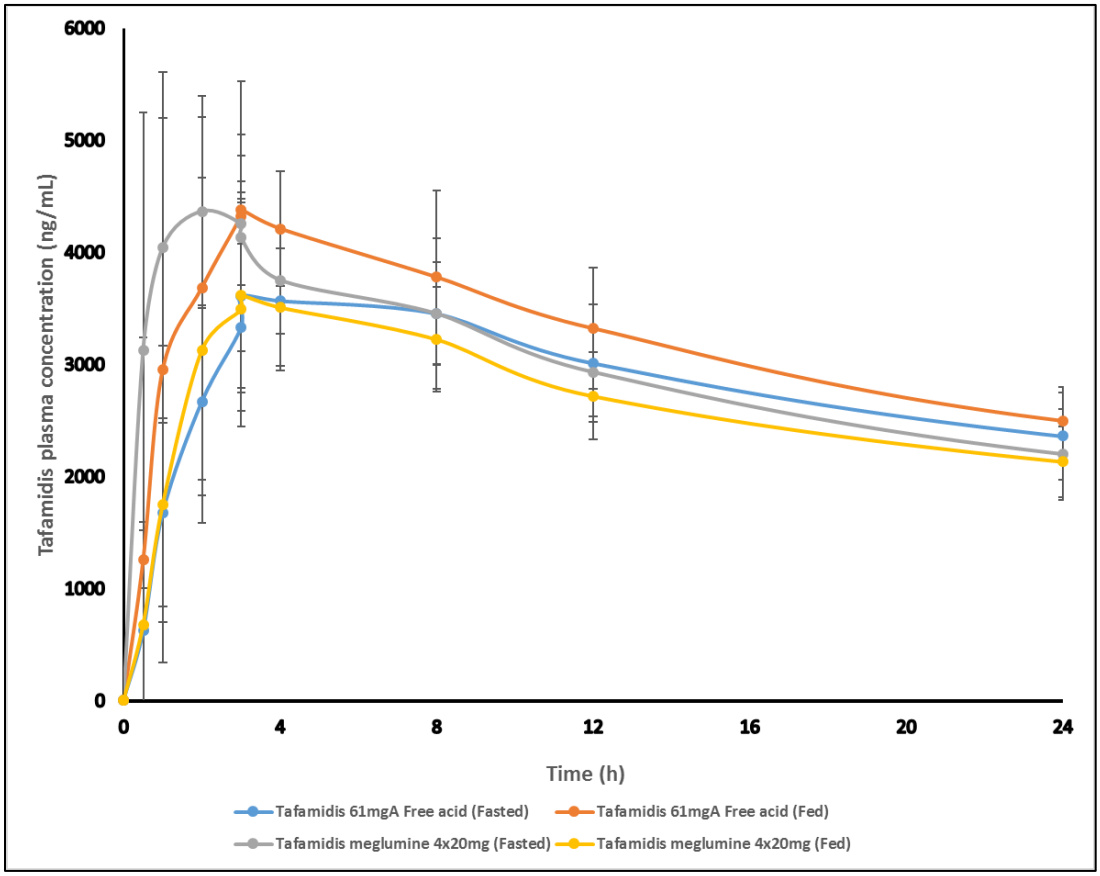
Single-dose relative bioavailability study

The Applicant conducted an open-label, randomized, 4-period, 4-sequence, crossover study in healthy adults (study B3461054) to evaluate the relative bioavailability of tafamidis free acid 61 mg compared to tafamidis meglumine 80 mg (4 x 20 mg tafamidis meglumine soft gelatin capsules), following administration of single oral dose. In the same study, the Applicant also

evaluated the effect of high-fat, high-calorie meal on the PK of tafamidis for both the capsule formulations and the results of that assessment are discussed earlier in section 3.3.4.

Mean plasma tafamidis concentration-time profiles following oral doses of tafamidis free acid 61 mg and tafamidis meglumine 4 × 20 mg under both fed and fasted conditions are presented in **Figure 3**.

Figure 3. Tafamidis mean plasma concentration-time profile following fed and fasted states administration of tafamidis free acid 61mg capsule and tafamidis meglumine 4 x 20 mg capsules



Source: Reviewer's analysis

Solid lines are mean tafamidis plasma concentration profiles. Error bars represent the standard deviation. Plasma PK samples were collected up to 168 h post-dose. The figure shows tafamidis plasma concentrations up to 24 h post-dose to show the differences between the mean concentration-time profiles around the peak plasma concentration of tafamidis

The systemic exposure ($AUC_{0\text{-inf}}$) of tafamidis is similar following fasted state administration of tafamidis free acid 61 mg and tafamidis meglumine 80 mg capsules, with the 90% CI of the Test/Reference ratio within the 80-125% bioequivalence range (**Table 4**). Mean C_{max} for tafamidis free acid 61 mg is 20% lower compared to that for tafamidis meglumine 80 mg (90% CI for Test/Reference ratio %: 72.8-87.4%). Median T_{max} is delayed by 1.5 hours for tafamidis

free acid 61 mg capsule (4.0 h (2.0-12.0 h)) compared to tafamidis meglumine 4 x 20 mg capsules (1.50 h (0.50-4.05 h)) following fasted state administration.

Table 4. Statistical summary of PK parameters from single-dose relative bioavailability and food effect study comparing tafamidis free acid 61 mg capsule versus tafamidis meglumine 80 mg (Study B3461054)

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

Source: Reviewer's analysis, CSR B3461054

Multiple-dose relative bioavailability study

The Applicant also conducted an open-label, randomized, 2-period, 2-sequence, crossover study (B3461056) in healthy adults comparing relative bioavailability of tafamidis free acid 61mg to tafamidis meglumine 80 mg (4 x 20 mg tafamidis meglumine soft gelatin capsules) following multiple once daily dose fasted state administration. The study demonstrated that following multiple dosing in fasted state, tafamidis steady state C_{max} and $AUC_{0\text{-}tau}$ for tafamidis 61 mg free acid capsule were not clinically significantly different (90% CI for test/reference ratio within 80-125%) to tafamidis meglumine 4 x 20 mg capsules (**Table 5**). Median T_{max} is delayed by 2 hours for tafamidis free acid 61 mg capsule (4.0 h (2.0-8.0 h)) compared to tafamidis meglumine 4 x 20 mg capsules (2.0 h (0.5-6.0 h)).

Table 5. Statistical summary of PK parameters from multiple-dose relative bioavailability study comparing tafamidis free acid 61 mg capsule versus tafamidis meglumine 80 mg (Study B3461056)

PK Parameter	Geometric Least Square Mean (%CV)		T/R Ratio (%) 90% C.I
	Tafamidis 61 mgA free acid capsule (Test) (n= 30)	Tafamidis meglumine 4 × 20 mg capsules (Reference) (n= 30)	
C_{max} (ng/mL)	8553 (23)	9087 (18)	94.1 (89.1, 99.4)
$AUC_{0\text{-}tau}$ (ng.h/mL)	170000 (23)	166200 (20)	102.3 (98.0, 106.8)

Source: Reviewer's analysis, CSR B3461056

Although the C_{max} of tafamidis is outside of the bioequivalence limit following a single dose, the multiple-dose study shows bioequivalence for tafamidis meglumine 80 mg and tafamidis free acid 61 mg at steady state for both C_{max} and AUC. Because of the long half-life of tafamidis and significant accumulation at steady state, the difference between the two formulations for the peak concentration trends to shrink at steady state and is generally expected for drugs with long life and significant steady state accumulation. Moreover, since the two dose levels, 20 and 80 mg, showed similar efficacy both in terms of primary and secondary endpoints from the ATTR-CM Phase 3 trial, any small changes in exposure to the extent seen in these relative bioavailability studies should not be clinically significant. Nevertheless, a 61 mg tafamidis free acid has 25% higher free acid compared to 80 mg tafamidis meglumine which contains 48.8 mg tafamidis free acid. This may result in higher local gastrointestinal tafamidis concentrations than what was tested in the ATTR-CM Phase 3 trial. During development, the Division remarked that it was important to understand the consequence of a possibly higher local gastrointestinal concentration on safety. The Division recommended the Applicant to generate safety data for tafamidis free acid 61 mg capsule formulation in the remainder of the then on-going phase 3 trial (B3461028) and the extension study (B3461045) (Refer: FDA Information Request letter dated 27 January 2017). In agreement with the Division, the Applicant proposed to replace the 4 x 20 mg tafamidis meglumine capsules in the Phase 3 ATTR-CM extension study (B3461045) with the tafamidis free acid 61 mg capsule formulation. Pending safety results from the on-going extension phase, there is adequate information to bridge 80 mg tafamidis meglumine and 61 mg tafamidis free acid formulations.

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