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.

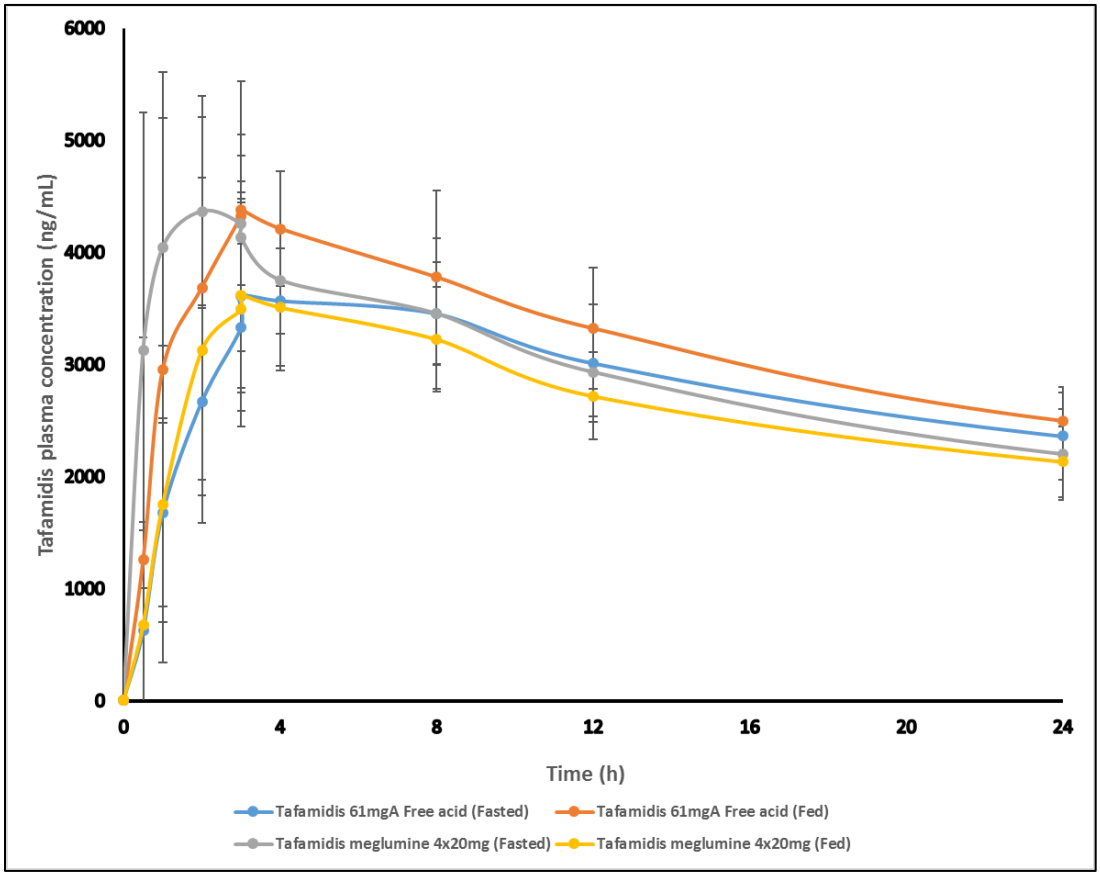
Single-dose relative bioavailability study

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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