

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211996Orig1s000**

**212161Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



IND 071880

**MEETING MINUTES**

FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.  
Attention: Nancy E. Martin, MBA  
Sr. Director, Worldwide Regulatory Strategy, Worldwide Safety and Regulatory  
445 Eastern Point Road  
Groton, CT 06340

Dear Ms. Martin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tafamidis meglumine.

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2018. The purpose of the meeting was to discuss the results of the tafamidis Phase 3 clinical program and your plans for NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Maryam Changi, Regulatory Project Manager at (240) 402-2725.

Sincerely,

*{See appended electronic signature page}*

Ellis Unger, MD  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** July 19, 2018, 09:00 am to 10:00 am, EDT  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Room: 1309  
Silver Spring, MD, 209903

**Application Number:** 071880  
**Product Name:** Tafamidis meglumine

**Indication:** For the treatment of transthyretin amyloidosis (ATTR) in adult patients with cardiomyopathy (due to wild type or variant TTR) to reduce mortality and cardiovascular-related hospitalization.

**Sponsor Name:** FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.

**Meeting Chair:** Ellis Unger, MD  
**Meeting Recorder:** Maryam Changi, PharmD

**FDA ATTENDEES**

\*Office of Drug Evaluation I:

Ellis Unger, MD, Director

\*Division of Cardiovascular and Renal Products:

Norman Stockbridge, MD, Director  
Martin Rose, MD, Clinical Team Leader  
Preston Dunnmon, MD, Clinical Reviewer  
Tzu-Yun McDowell, PhD, Clinical Reviewer  
Jean Wu, PhD, Non-Clinical Team Leader (Acting)  
William Link, PhD, Non-Clinical Reviewer  
Edward Fromm, RPh, RAC, Chief, Project Management Staff  
Maryam Changi, PharmD, Regulatory Project Manager

\*Office of Clinical Pharmacology:

Sudharshan Hariharan, PhD, Team Leader  
Snehal Samant, PhD, Reviewer

\*Office of Pharmaceutical Quality:

Wendy Wilson- LEE, PhD, CMC Branch Chief  
Mariappan Chelliah, PhD, CMC Reviewer

\*Division of Medication Error Prevention and Analysis:

Chi-Ming (Alice) Tu, PharmD, Team Leader  
Maximilian Straka, PharmD, Reviewer

\*Office of Clinical Outcome Assessment team:

Selena Daniels, PharmD, MS, Team Leader

**SPONSOR ATTENDEES**

Alexandra Barsdorf, PhD, Director, Outcomes & Evidence  
Brenda Cooperstone, MD, Senior Vice President, Chief Development Officer, Rare Disease  
Balarama Gundapaneni, MS, FSP, Statistician, Statistics  
Peter Huber, RPh, Director, Safety Risk Management  
Iwona Jeske Dupont, PhD, Vice President, Global Regulatory Strategy, Rare Disease  
HuiHua Li, MD, MS, Associate Director, Statistics  
Nancy Martin, MBA, Senior Director, US Regulatory Lead  
Christopher McCawley, VMD, Senior Director, Global Regulatory Lead  
Terrell Patterson, RPh, Director, Clinical  
Steve Riley, PharmD, PhD, Senior Director, Clinical Pharmacology & Pharmacometrics  
Jeffrey Schwartz, PhD, Senior Director, Statistics  
Sandi See Tai, MD, Asset Team Lead  
Marla Sultan, MD, MBA, Executive Director, Global Clinical Lead

**1.0 BACKGROUND**

The Sponsor claims that tafamidis is a stabilizer of the tetrameric form of wild type and amyloidogenic variants of transthyretin (TTR). Tafamidis is said to bind to TTR at the thyroxine binding site and inhibit TTR tetramer dissociation, the rate-limiting step in the amyloidogenic process. Tafamidis meglumine 20-mg capsules have been approved outside the US for the treatment of transthyretin amyloidosis (ATTR) in adult patients.

Tafamidis was granted Orphan Designation for the treatment of symptomatic ATTR cardiomyopathy (ATTR-CM) on February 17, 2017. The drug was also granted Fast Track Designation and Breakthrough Designation for this indication on May 17, 2017 and May 18, 2018, respectively.

Pfizer intends to submit a New Drug Application (NDA) based on the results of Study B3461028. Pfizer claims that the study met its primary and key secondary objectives and the results showed that the administered doses of tafamidis meglumine, 20 mg and 80 mg, seem similar with respect to overall efficacy and safety.

Pfizer requested this type B, pre-NDA meeting to discuss and reach agreement on the structure, format, and data presentation for the tafamidis ATTR-CM, NDA #211996, as well as to highlight the results from the pivotal Study B3461028.

FDA sent Preliminary Comments to FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer Inc. on July 17, 2018. The Sponsor used the appended slides to lead the discussion.

## 2. DISCUSSION

### 2.1. eCTD Content and Format

**Question 1:** *Does the Agency agree with the proposed eCTD content and format and dataset conventions summarized in this briefing document for the tafamidis ATTR-CM NDA #211996?*

**FDA Response to Question 1**

Your proposal to submit *the tafamidis ATTR-CM NDA #211996*, organized in eCTD format in accordance with the cited FDA guidances, is acceptable.

**Discussion:**

No further discussion.

### 2.2. Non-Clinical

**Question 2:** *Does the FDA agree that the nonclinical program as summarized in this briefing document supports the nonclinical review of the tafamidis ATTR-CM NDA #211996?*

**FDA Response to Question 2:**

Yes, we believe that the nonclinical data summarized supports the nonclinical review of the NDA(s). Please see the following comments for the nonclinical data submission.

1. As noted in the briefing document, the nonclinical data under IND 071880 were previously submitted and reviewed as part of NDA 202737. The summary tables (Table 5, 8, 9) listed the number of each study but did not list the IND/NDA numbers to which the studies were submitted. To locate the studies and the previous reviews easily, please add the IND/NDA numbers to each study.
2. You indicated that the rat carcinogenicity study #805917 will be included in the NDA. We located the written report of this carcinogenicity study; however, we could not find the SAS XPT datasets. Please clarify whether the datasets have been submitted.
3. In your briefing document, you indicated that three Reverse Mutation Assays of starting materials (Study # 504677 and # 507970) and metabolite (#504698) were conducted. If they have already been submitted, please direct us to their location.

**Discussion:**

No further discussion.

**2.3. Clinical Pharmacology/ Pharmacometrics**

**Question 3:** *Does the Agency agree that the proposed clinical pharmacology data package as outlined in this briefing document supports the clinical pharmacology and biopharmaceutics review of the tafamidis ATTR-CM NDA #211996?*

**FDA Response to Question 3:**

Yes, we agree that the proposed clinical pharmacology package supports the clinical pharmacology and biopharmaceutics review of NDA211996. We have the following additional comments:

1. Bioanalytical method validation reports supporting the clinical studies are currently not listed in the Summary table section 5.3.1.4. Please submit the associated bioanalytical and method validations reports for the clinical studies listed in the data package.

**Discussion:**

No further discussion.

2. Your briefing package reads “PF-06291826-00 has the potential to inhibit breast cancer resistance protein (systemically and in the gastrointestinal tract), and OAT3 at clinically relevant concentrations.” Based on this assessment, do you plan to conduct clinical studies to address the interaction potential with BCRP and OAT3?

**Discussion:**

The Sponsor referred to slide 22 and explained that the increase in AUC of the substrate is expected to be less than 24% and therefore inhibition of OAT3 is not considered to be clinically relevant. The Division asked the Sponsor whether the expected change in AUC was based on PBPK modeling. The Sponsor clarified that they are using the in vitro criterion (I/IC<sub>50</sub> or R-value, as outlined in the Draft In Vitro DDI Guidance) to project the expected increase in AUC. The Division clarified that the in vitro criterion is just a decision-making tool for whether a clinical DDI study should be conducted and should not be used as a quantitative metric to assess the magnitude of a potential interaction. The Division told the Sponsor that if the in vitro criterion suggests the likelihood for an interaction, then the in vivo DDI study would be needed, but agreed with the Sponsor that the study can be conducted as a post marketing requirement.

The Sponsor also clarified that use of OAT3 substrates was not an exclusion criterion for the Phase 3 study and that they were not aware whether any of the patients were taking OAT3 substrates during the study.

The Division mentioned that using the adverse event profile from a phase 3 study to assess a DDI is not sensitive, but agreed to review such information.

## 2.4 Efficacy

**Question 4:** *Does the Agency agree with the presentation proposed for the Summary of Clinical Efficacy (SCE) in the tafamidis ATTR-CM NDA #211996, specifically that the SCE will focus upon efficacy data from pivotal study B3461028, which is pertinent to the claimed indication in ATTR-CM,* [REDACTED] (b) (4)

**FDA Response to Question 4:**

What you propose is acceptable.

**Discussion:**

No further discussion.

**Question 5:** *In lieu of an Integrated Summary of Efficacy (ISE), does the Agency agree to the rationale and proposed mapping of the ISE with cross references to the SCE and other relevant sections of the eCTD, as outlined in this briefing document in support of the efficacy review of tafamidis ATTR-CM NDA #211996?*

**FDA Response to Question 5:**

What you propose is acceptable.

**Discussion:**

No further discussion.

**Question 6:** *Based on similar clinical efficacy and safety profiles across the 20 and 80 mg doses and biomarker data that suggest some increased benefit of the 80-mg dose compared to the 20-mg dose, Pfizer proposes a dose recommendation of 80 mg tafamidis meglumine daily (4 × 20 mg tafamidis meglumine or equivalent 61 mg tafamidis free acid) for patients with ATTR-CM. Patients who are not able to tolerate a dose of 80 mg may be administered 20 mg tafamidis meglumine. This dose recommendation will be implemented in the Early Access Program (EAP); does the Agency agree with this proposal?*

**FDA Response to Question 6:**

We are uncertain about starting all subjects on the highest dose, although we understand that you continue to analyze and present your data to support this strategy.

**Discussion:**

The Sponsor referred to slides 4 thru 13 and explained the rationale behind using the 80-mg dose over 20 mg. The arguments made in favor of starting all subjects on the highest dose are based on the following observations:

- The majority of subjects studied in the clinical program received 80 mg
- There appeared to be no dose-related safety considerations
- Baseline NT-proBNP was predictive of mortality

- There was a numerically greater reduction of the placebo-corrected change from baseline of NT-proBNP in the 80-mg arm compared to the 20-mg arm that was nominally significant in post hoc analysis.

Given these observations and in light of the progressive, fatal nature of this disease, the Sponsor believes it would be better for physicians to start with the higher dose and maintain this if tolerated. The Division understands this rationale, but also notes that:

- The Sponsor has found that ongoing Exposure-Response Modeling Analysis does not differentiate between doses for clinical endpoints
- On-treatment NT-proBNP trends have not consistently mirrored CV outcome endpoint trends in large heart failure trials
- More subjects discontinued drug due to TEAEs in the 80-mg arm (23% versus 18%).

## 2.5. Safety

***Question 7:*** Does the Agency agree that the proposed content and presentation of the Summary of Clinical Safety (SCS) as summarized in this briefing document supports the clinical safety review of tafamidis meglumine ATTR-CM NDA# 211996?

**FDA Response to Question 7:**

What you propose is acceptable.

**Discussion:**

No further discussion.

***Question 8:*** Does the Agency agree that the proposed list and presentation of adverse events of special interest (AESI) as outlined below and in the overview of the tafamidis Integrated Analysis Plan (Appendix 7) supports the clinical safety review of tafamidis meglumine ATTR-CM NDA #211996?

**FDA Response to Question 8:**

In general, the proposed list and presentation of AESI seems reasonable. However, we note that your hypersensitivity definition is based on the narrow-scope SMQ which will not include some pulmonary adverse events LLTs such as asthma, shortness of breath or wheezing. We suggest that you include all such pulmonary adverse event LLTs in your search for hypersensitivity.

You have proposed to present safety assessments in different cohorts based upon the phase and population studied including a cohort with all tafamidis-treated patients diagnosed with ATTR-CM. You also proposed to summarize AEs and SAEs by incidence and exposure-adjusted incidence rate in both ISS/SCS. Overall, we agree with your integrated analysis plan. Please submit your SAS programs for the primary safety analyses for cohort 4.

**Discussion:**

The Sponsor referred to slide 23. The Division agreed with the Sponsor's proposed modifications to the LLTs that will contribute to the definition of hypersensitivity, and specifically to the addition of those LLTs suggesting pulmonary manifestations of allergy. The Division noted that the basic terms "shortness of breath" and "dyspnea" are still missing from the proposed list, but acknowledged that these symptoms may decrease based on the efficacy effects of tafamidis. The Sponsor indicated that preliminary assessments of their data suggest that shortness of breath and dyspnea did in fact decrease in the tafamidis treatment arm which led the company to omit these terms from the SMQ definition for hypersensitivity. This being the case, the Division agreed with the Sponsor's rationale for not including these two LLTs in the definition of hypersensitivity.

**Question 9:** *Does the Agency agree that the proposed content and presentation of the Integrated Summary of Safety (ISS) as outlined in this briefing document supports the clinical safety review of tafamidis meglumine ATTR-CM NDA #211996?*

**FDA Response to Question 9:**

Yes, what you propose is acceptable.

**Discussion:**

No further discussion.

**Question 9a:** *Specifically, does the Agency agree with the proposed presentation of the Phase 1 safety data, the Phase 2 and 3 ATTR-CM safety data for the ISS, and safety information from the ongoing B3461045 and B3461026 studies as outlined in this briefing document?*

**FDA Response to Question 9a:**

Yes. The accuracy of your adverse event analyses is critically dependent on your translation of verbatim terms to preferred terms. As part of FDA's assessment of your NDA, our staff will check your translations for accuracy. At your earliest convenience, please submit to the IND a SAS transport file containing, for each adverse event in your development program, two columns of information: the verbatim term and the preferred term. Other information (subject ID, age, treatment, etc.) is not needed at this time.

**Discussion:**

The Sponsor confirmed that the SAS transport file is being prepared and will be submitted to the IND.

**Question 10:** *Pfizer proposes to include CRFs and narratives for all SAEs, deaths, discontinuations due to AEs, and pregnancies for all completed and ongoing tafamidis (ATTR-CM and ATTR-PN) clinical studies. Does the Agency agree with the proposed narrative plan (Appendix 10) and that the presentation of safety narratives for the tafamidis studies supports the clinical safety review of tafamidis ATTR-CM NDA 211996?*

**FDA Response to Question 10:**

Yes. Please also provide a table that lists the IDs for subjects who died, who had SAEs, who discontinued because of an AE. The subject IDs in the table should hyperlink to the respective narratives.

**Discussion:**

No further discussion.

**Question 11:** *In light of the similar safety profile between the 20 mg and 80 mg doses and*

(b) (4)

**FDA Response to Question 11:**

No, you should submit a Safety Update for data from your ongoing studies in ATTR-CM or ATTR-PN collected after the safety data cut-off date for the ISS.

**Discussion:**

The Sponsor told the Division that there will be 200 subjects in the OLE study and will start at the end of August this year. For uncontrolled data, the Division suggested the Sponsor conduct time-to-event (Kaplan-Meier) analyses of adverse events. An update of post-marketing safety for the (b) (4) should likewise be provided.

The Sponsor told the Division that they plan to submit the NDA by November this year. The Division encouraged the Sponsor to submit some of the components earlier. The Sponsor confirmed that non-clinical data, the clinical study report for the phase 3 trial, and some individual study datasets will be submitted earlier.

## 2.6. Expanded Access

**Question 12:** *Does the Agency agree with the overview of our Early Access Program (EAP) plans for tafamidis ATTR-CM as described in this briefing document?*

**FDA Response to Question 12:**

Yes, we agree.

**Discussion:**

No further discussion.

## 2.7. Regulatory/ Administrative

**Question 13:** *Does our proposal for the contents of NDA #212161 for the tafamidis 61 mg free acid formulation, with its substantial cross-referencing to NDA#211996, address the Regulatory need for separate NDAs for tafamidis free acid and for tafamidis meglumine?*

**FDA Response to Question 13:**

Yes.

**Discussion:**

No further discussion.

**Question 14:** *At the time of our submission we will not have B3461045 patient exposure for the commercial 61 mg tafamidis free acid formulation; however, now that the bioequivalence of 80 mg tafamidis meglumine (4 × 20 mg) with 61 mg tafamidis has been established, an amendment to Protocol B3461045 is underway which transitions patients currently on 80 mg tafamidis meglumine to 61 mg tafamidis free acid. With the implementation of this protocol amendment in 4Q2018, we would anticipate submitting safety data (all-causality SAEs table /narratives and all-causality TEAEs) by April 2019 on approximately 40 patients exposed to 61 mg tafamidis free acid for 3 months. Given the overall safety profile with tafamidis, does the Division agree that the provision of the B3461045 safety data as proposed would address the Division's request for patient exposure data to 61 mg and further, that this could be considered a minor amendment?*

**FDA Response to Question 14:**

We are unlikely to delay regulatory action for the 20-mg product awaiting safety data for the 61-mg formulation.

**Discussion:**

The Sponsor referred to Slide 14 to ask clarifying questions. The Division told the Sponsor that the 61-mg NDA will not be receive a priority review; however, the Division will do what it can to finish the review quickly. The Division agreed that the Sponsor's proposed clinical experience for 61-mg is sufficient to support the NDA approval if it is similar. The Division told the Sponsor that the amendment in the last third of the review of the 61-mg NDA would not have any impact on the review and would not change the approval timeline.

**Question 15:** *Study B3461028 has demonstrated the robust efficacy of tafamidis in the treatment of ATTR amyloidosis in adult patients with cardiomyopathy (wild type or variant ATTR), a devastating disease for which there is currently no effective pharmacological treatment. With the 4Q2018 submission of the tafamidis ATTR-CM NDA #211996, Pfizer plans to include a request for Priority Review. Does the Agency anticipate assigning Priority Review to NDA #211996?*

**FDA Response to Question 15:**

Yes.

**Discussion:**

No further discussion.

**Question 16:** *For the Bioresearch Monitoring (BIMO) inspections of clinical data for the tafamidis ATTR-CM NDA #211996, Pfizer will provide the list of investigators, data listings*

*and datasets for pivotal study B3461028. Does the Division agree that the proposed contents of the BIMO as outlined in this briefing document will support clinical review of the tafamidis ATTR-CM NDA #211996?*

**FDA Response to Question 16:**

Yes, we agree. Although not required, we also encourage submission of the Summary-level Clinical Site Dataset as outlined in the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>) to facilitate selection of clinical sites for inspection.

**Discussion:**

No further discussion.

**Question 17:** *Per 21 CFR 314.55 (d), Pfizer claims exemption from the requirement of conducting a pediatric program due to the orphan drug status of tafamidis meglumine for the treatment of ATTR amyloidosis in adult patients with cardiomyopathy (wild type or variant ATTR). We are therefore not planning to include a Pediatric Waiver in NDA #211996. Is the Division aligned with this approach?*

**FDA Response to Question 17:**

Yes.

**Discussion:**

No further discussion.

**Question 18:** *Provided Priority Review is assigned to tafamidis ATTR-CM NDA #211996 and as an Orphan Drug Product with Fast Track Designation and Breakthrough Therapy designation that has demonstrated robust efficacy in the reduction of [REDACTED] (b) (4) CV-related hospitalization and a tolerable safety profile, Pfizer would appreciate the Division's thoughts as to the need for an Advisory Committee Meeting for tafamidis ATTR-CM NDA# 211996.*

**FDA Response to Question 18:**

An AC meeting is unlikely to be needed.

**Discussion:**

No further discussion.

**Additional comment:**

We note that you have a hierarchical analysis plan that includes the KCCQ Overall score. We prefer endpoints that can be clearly communicated and are meaningful to the patients and prescribers to support drug labeling. The KCCQ Overall score 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. We believe that the KCCQ Total Symptom score and KCCQ Physical Limitation score are more meaningful and

interpretable to support labeling. We recommend that you also include results for these two KCCQ scores in your planned NDA submission. We also recommend that you include empirical cumulative distribution function (eCDF) and probability density function (PDF; often estimated using kernel density estimation) curves of the KCCQ score changes from baseline by treatment arms to help interpret the treatment outcomes. The additional analyses described here do not need to be included in the hierarchical analysis plan.

**Discussion:**

The Sponsor referred to slide 17 and reminded the Division that the use of KCCQ overall summary score as a secondary endpoint was part of the SPA agreement and agreed to provide analyses requested within the KCCQ PRO evidence dossier.

The Division acknowledged the additional data presented related to the KCCQ Total Symptom and Physical Limitations scores and will review further in the NDA submission.

The Division also requested that the Sponsor include data on missingness in their submission. The Division suggested that the Sponsor explore different approaches to present PRO data for ease of interpretation (e.g., presenting the distribution of responses in a histogram).

**3.0 OTHER IMPORTANT MEETING LANGUAGE:**

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

#### **4.0 ATTACHMENTS AND HANDOUTS**

Sponsor's slides are attached.

24 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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ELLIS F UNGER  
08/15/2018



IND 071880

**MEETING PRELIMINARY COMMENTS**

Pfizer

Attention: Christopher L. McCawley, M.S., V.M.D.  
Senior Director, Worldwide Regulatory Strategy, Worldwide Safety and Regulatory  
445 Eastern Point Road  
Groton, Connecticut 06340

Dear Mr. McCawley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tafamidis Soft Gelatin Capsules for TTR-CM.

We also refer to your March 16, 2018, correspondence, requesting a meeting to discuss questions related to Chemistry, Manufacturing, and Controls content of the NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (240) 402-7765.

Sincerely,

*{See appended electronic signature page}*

Grafton G Adams R.N., M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

ENCLOSURE:

Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## PRELIMINARY MEETING COMMENTS

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 21, 2018 10:00 a.m.  
**Meeting Location:** Teleconference

**Application Number:** 071880  
**Product Name:** Tafamidis Soft Gelatin Capsules

**Indication:** Transthyretin amyloidosis cardiomyopathy (TTR-CM)  
**Sponsor/Applicant Name:** Pfizer

**Introduction:** This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Monday, May 21, 2018 between Pfizer and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Business Project Manager (RBPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

### 1.0 BACKGROUND

Transthyretin (TTR) is a circulating tetrameric protein produced by the liver. If the TTR subunits dissociate, they can become insoluble and form amyloid fibrils in various target organs that leads to a spectrum of disease, the two major phenotypes being polyneuropathy and cardiomyopathy. Tafamidis meglumine 20 mg capsules have been approved in several markets outside of the US for Transthyretin Familial Amyloidosis Polyneuropathy (TTRFAP) (EU and other markets, Brazil, Argentina, Israel, Japan, Macau, Macedonia, Mexico, Russia, and South Korea). An NDA is planned for the cardiac manifestation of transthyretin cardiomyopathy (TTR-CM).

Tafamidis was assigned ODD #12-3633 for the treatment of patients with TTR-CM due to wild-type or variant TTR to reduce cardiovascular hospitalization and mortality. Both tafamidis meglumine 20 mg and tafamidis 61.0 mg are being studied under IND # 71,880 for this

indication. Depending on the outcome of the clinical study, the NDA may provide for both of these strengths/formulations (i.e. tafamidis meglumine 20 mg soft gelatin capsules and tafamidis 61.0 mg soft gelatin capsules). The NDA is planned for 4Q2018.

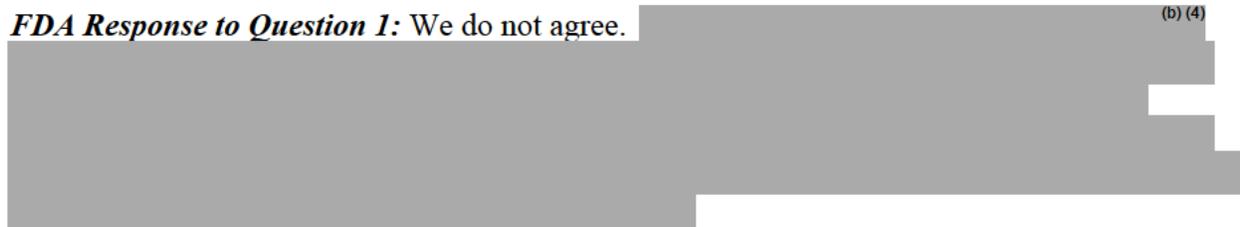
Pfizer requested to meet with the quality review team to orient them on the CMC portion of the NDA and discuss three CMC questions related to the provision of CMC content.

## 2.0 DISCUSSION

***Question 1: Tafamidis was assigned ODD #12-3633 for the treatment of patients with TTR-CM due to wild-type or variant TTR to reduce cardiovascular hospitalization and mortality. Both tafamidis meglumine 20 mg and tafamidis 61.0 mg are being studied under IND # 71,880 for this indication.***



***FDA Response to Question 1: We do not agree.***



***Question 2:*** Due to the potential for an earlier submission to the Agency, the sponsor would like to discuss a proposed approach for providing drug product stability data in the original NDA as follows:

- ***Tafamidis meglumine 20 mg soft gelatin capsules:***
  - ***30 months of long term (25°C/60 % RH, 30°C/75% RH and 5°C/ambient RH) and 6 months of accelerated (40°C/75%RH) stability data on 3 batches***
  - ***9 months of long term (25°C/60 % RH) and 6 months of accelerated (40°C/75%RH) stability data on an additional 3 batches of tafamidis meglumine 20 mg capsules (manufactured using drug substance from the proposed commercial supplier).***
  
- ***Tafamidis 61.0 mg soft gelatin capsules:***
  - ***9 months of long term (25°C/60 % RH, 30°C/75% RH and 5°C/ambient RH) and 6 months of accelerated (40°C/75%RH) stability data on 3 batches.***

***Pfizer proposes to submit additional stability data for the tafamidis 61.0 mg soft gelatin capsules from the 12 month time point during the review period (within 30 days of submission).***

- a) ***Does the Agency agree with the proposed stability strategy above?***
  
- b) ***Does the Agency agree that submission of the 12 month DP stability data during the NDA review (within 30 days of submission) is acceptable and will not extend the regulatory review period?***

***FDA Response to Question 2:*** Your proposal to include at least 30 months of long term and 6 months of accelerated stability data for the tafamidis meglumine 20 mg soft gelatin capsules is acceptable. However, your proposal to include only 9 months of long term and 6 months of accelerated stability data for the tafamidis 61.0 mg soft gelatin capsules is not acceptable. In accordance with ICH Q1A(R2) Guidance, a minimum of 12 months of long-term stability data should be included in initial submission of the NDA.

We note the recent submission to the Agency requesting breakthrough therapy designation. If the Agency grants breakthrough designation, we would accept your proposal to submit the NDA with 9 months of long-term data and 6 months of accelerated data with the commitment to submit additional long-term stability data through 12 months storage within 30 days of initial submission for the tafamidis 61.0 mg soft gelatin capsules.

***Question 3: NDA 202737 for tafamidis meglumine 20 mg soft gelatin capsules for the treatment of TTRFAP was submitted on 16 December 2011 and accepted by FDA on 13 February 2012. The Sponsor received a Complete Response Letter (CRL) on 15 June 2012***

(b) (4)

***For the tafamidis 61.0 mg soft gelatin capsules, the dissolution method development and strategy for setting the acceptance criteria will be summarized in this meeting briefing package.***

- a) Does the Agency have any comments on the dissolution method and the strategy for setting the acceptance criteria as outlined in the briefing package?***

**FDA Response to Question 3:** On its face, your approach for selecting the dissolution method and acceptance criterion for the 61.0 mg soft gelatin capsules appears to be reasonable.

If you prefer to get the FDA's feedback on acceptability of the proposed dissolution method, you may submit a detailed dissolution method development report as an IND amendment and state in the cover letter that the FDA's review for acceptability of the dissolution method is being requested. Alternatively, acceptability of the dissolution method can be determined during NDA review. Please refer to 'Additional Biopharmaceutics Comments' for information that should be provided in the dissolution method development report, and for general comments regarding setting up dissolution acceptance criterion.

**Additional Biopharmaceutics Comments:**

The FDA has the following recommendations regarding the dissolution information (method and acceptance criterion) that should be provided in the submission.

**Dissolution Method:** Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the following information in the dissolution method development report:

- a. Solubility data of the drug substance over the physiologic pH range.
- b. Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions associated with each method development study should be clearly specified. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 5, 10, 15, 20, 30, 45 60, etc. min).
- c. Data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters

(e.g.,  $\pm$  10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g.,  $f_2$  values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method can reject product that is not bioequivalent to the reference-target drug product.

- d. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.
- e. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc. For general recommendations on method validation, refer to the USP Chapters “The Dissolution Procedure: Development and Validation” <1092> and “Validation of Compendial Methods” USP Chapter <1225>.
- f. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). The dissolution data should be reported as the cumulative percentage of drug dissolved (the percentage is based on the drug product’s label claim). For the submission of the dissolution data, refer to data presentation below.

**Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

- a. The multi-point dissolution data (n=12, sampling every 2 hours) from the pivotal clinical/PK drug product-batches and primary registration batches should be used for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits).
- b. The in vitro dissolution profile should be complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).
- c. The dissolution acceptance criterion should be based on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).
- d. The selection of the sampling time point should be where Q = 80 % dissolution occurs.
- e. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

**Dissolution Data Presentation:** In the dissolution method development report, present detailed experimental dissolution data as follows:

- In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.

- In addition to the mean dissolution data presented in graphical and tabular formats, submit in the “Batch Analysis” section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel “.xls or .xlsx” format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
- Provide in your IND/NDA the dissolution data as described in the example below.

### Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Cell A2 – blank

Individual Unit Number (starting from cell A3 numerical values signifying the test unit)

Use one sheet for each unique batch/lot. Label accordingly in Cell A1

Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))

Dissolution Data (starting from cell B3 numerical values indicating percent drug release)

Sheet1 Sheet2 Sheet3

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GRAFTON G ADAMS  
05/16/2018

# CDER Breakthrough Therapy Designation Determination Review Template

<b>IND/NDA/BLA #</b>	IND 071880
<b>Request Receipt Date</b>	04/03/2018
<b>Product</b>	Tafamidis meglumine
<b>Indication</b>	Tafamidis is indicated for the treatment of transthyretin (TTR) amyloidosis in adult patients with cardiomyopathy (due to wild type or variant TTR) to reduce the <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> cardiovascular hospitalization.
<b>Drug Class/Mechanism of Action</b>	Tafamidis is an orally administered small molecule which, by tightly binding to the thyroxine binding sites on the TTR tetramer, is thought to prevent destabilization into the monomeric form. Biochemical evidence shows that TTR tetramer dissociation into monomers is the rate-limiting step for the entire amyloid cascade. Slowing TTR dissociation into monomers is expected to reduce the formation of downstream toxic aggregates and delay the pathophysiologic processes that are hallmarks of TTR amyloidosis.
<b>Sponsor</b>	Foldrx Pharmaceuticals (a Pfizer subsidiary)
<b>ODE/Division</b>	ODE 1/ Division of Cardiovascular and Renal Products
<b>Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)</b>	May 31, 2018

*Note: This document must be uploaded into CDER’s electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

**Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The intended indication for Tafamidis is the treatment of transthyretin (TTR) amyloidosis in adult patients with cardiomyopathy (due to wild type or variant TTR) to reduce the combination of all-cause mortality and cardiovascular hospitalization.

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

YES  NO

- Was the BTDR submitted to a PIND?**

YES  NO

If “Yes” do not review the BTDR. The sponsor must withdraw the BTDR. BTDR’s cannot be submitted to a PIND.

*If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:*

- Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening<sup>1</sup>?

YES  NO

***If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:***

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- YES the BTDR is adequate and sufficiently complete to permit a substantive review  
 Undetermined  
 NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

**5. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

***If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.***

***If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.***

**6. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.**

Transthyretin (TTR) amyloidosis can present as either a hereditary or an age-related disease. A mutation in TTR (a 127-amino acid, 55 kDa protein that is primarily synthesized in the liver and is a transporter of thyroxine and retinol-binding protein-retinol (vitamin A) complex) or age-related changes in TTR accelerates the process of fibrillogenesis whereby the tetrameric structure of the TTR protein dissociates leading to amyloid deposition primarily in heart tissue causing TTR cardiomyopathy (TTR-CM). Symptoms of TTR-CM are typical of restrictive cardiac disease (HFpEF) and include dyspnea on exertion, orthostatic hypotension, syncope, and conduction abnormalities, including bundle branch block, atrioventricular block, sinoatrial block, and atrial fibrillation. Symptoms are not mutation-type dependent. Objective measures of cardiac involvement are nonspecific for TTR-CM include abnormal electrocardiogram with findings including low voltage, left and right ventricular wall thickening by echocardiogram, and elevated cardiac biomarkers.

TTR-CM is a slowly progressive disease, often diagnosed late in the disease process because it is not readily distinguished from more common causes of HFpEF (hypertension, diabetes, ischemia and aging). At time of diagnosis, patients often have marked ventricular wall thickening, profound diastolic dysfunction, and conduction abnormalities. Median survival from diagnosis for patients with TTR-CM was reported as 41 months in a study of the Val122Ile TTR mutation and 46 months for wild-type (age-related)<sup>3</sup>. Death in most patients with cardiac amyloidosis is from cardiac causes, including fatal arrhythmia, heart failure, and myocardial infarction. The prevalence of transthyretin cardiomyopathy is presently unknown; however, it is estimated (because of relatively high prevalence in autopsy series) that less than 1% of people with the disease are diagnosed.

Except for symptom management, such as use of diuretics for symptoms of heart failure and pacemaker placement for cardiac arrhythmias, the only treatment option currently available (for only those TTR-CM patients who may be able to tolerate it) is orthotopic heart and/or liver transplant. Transplantation of the liver removes the primary production site of amyloidogenic mutant TTR protein and replaces it with the production of wild-type TTR. Because no pharmacotherapy has been approved for the treatment of TTR-CM, a serious and fatal medical condition, there is a clear unmet medical need for other treatment options.

Most hereditary TTR-amyloidosis patients develop nervous system involvement with or without cardiac amyloidosis.

Tafamidis is an orally administered small molecule, under development by Pfizer, as a disease modifying therapy for TTR amyloid diseases. It binds to the thyroxine binding sites on the TTR tetramer, thereby preventing destabilization into the monomeric form. It binds to the 2 thyroxine binding sites with negative cooperativity, exhibiting dissociation constants of 2 nM [Kd1] and 154 nM [Kd2]<sup>4</sup> and kinetically stabilizing the TTR tetramer when bound.<sup>5</sup>

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<sup>3</sup> Connors LH, Doros G, Sam F, et al, Clinical features and survival in senile systemic amyloidosis: comparison to familial transthyretin cardiomyopathy, *Amyloid*. 2011;18(sup1):157-159. doi:10.3109/13506129.2011.574354059.

<sup>4</sup> DeVit M, Wang L, Weigel C, et al. In vitro profile of Fx-1006A, a novel, potent and selective transthyretin (TTR) stabilizer. Proceedings of the 11th International Symposium on Amyloidosis; 5-9 Nov 2006; Woods Hole, MA, USA (Abstract).

<sup>5</sup> Sekijima Y et al. Familial Transthyretin Amyloidosis, 2009 [www.ncbi.nlm.gov/books/NBK1194](http://www.ncbi.nlm.gov/books/NBK1194) PMID2030173.

Substantial biochemical evidence shows that TTR tetramer dissociation into monomers is the rate-limiting step for the entire amyloid cascade.<sup>6</sup> Therefore, slowing TTR dissociation into monomers is expected to reduce the formation of downstream toxic aggregates and delay the pathophysiologic processes that are hallmarks of TTR amyloidosis.

In February 2012, tafamidis meglumine received orphan drug designation (#12-3633) for the treatment of symptomatic TTR with cardiomyopathy due to wild-type or variant TTR to reduce cardiovascular hospitalization and mortality.

On May 2017, tafamidis meglumine received Fast Track designation for the treatment of symptomatic TTR with cardiomyopathy due to wild-type or variant TTR to reduce cardiovascular hospitalization and mortality.

Tafamidis meglumine received a Marketing Authorization in the EU under exceptional circumstances on 16 November 2011 and is currently approved in 40 countries. The approved indication in the EU is for the treatment of transthyretin amyloidosis (ATTR) in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. In March 2018, the Ministry of Labor Health and Welfare in Japan granted tafamidis meglumine expedited review designation for this indication.

In the US tafamidis meglumine received Orphan Drug designation [REDACTED] (b) (4) [REDACTED] Fast Track for this indication in September 2006. An NDA for the polyneuropathy indication was submitted in February 2011 and received a Refuse to File letter in March 2011. The NDA was resubmitted in December 2011 and received a Complete Response Letter in June 2012. FDA has engaged with the sponsor since then to find a potential path forward. It appears that the development program in TTR-amyloid polyneuropathy is currently inactive.

#### **8. Information related to endpoints used in the available clinical data:**

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary endpoint of a recently completed, phase 3 placebo-controlled RCT that the sponsor is using to support their BTDR is a combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared to placebo at 30 months.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

All-cause mortality and frequency of cardiovascular-related hospitalizations are accepted by the Division as clinically significant outcome measures. Quality of life measures would also be acceptable if the drug were shown to influence the disease process and the effect size were deemed clinically meaningful. Exercise capacity or actigraphy might be acceptable outcome measures for full approval if the difference between treatment groups was thought to be clinically meaningful.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Currently there are no biomarkers that the Division can rely upon independently to predict clinical benefit in heart failure.

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<sup>6</sup> Redondo C, Damas AM, Saraiva MJ. Designing transthyretin mutants affecting tetrameric structure: implications in amyloidogenicity. *Biochem J* 2000;348 Part 1:167– 72.

**9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.**

There are no approved therapies for TTR-CM.

**10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>7</sup>.**

There have been three other requests for BTDR in related conditions.



**11. Information related to the preliminary clinical evidence:**

**a. Table of clinical trials supporting the BTDR**

Study ID	Phase/ Trial Design	Trial endpoints	Treatment Groups	Number enrolled	Results
B3461028	Phase 3 international, multicenter, double-blind, placebo-controlled, randomized, 3-arm clinical study in 441 patients that investigated the efficacy,	Primary: combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared to placebo at 30 months	Tafamidis meglumine capsules 20 mg, 80 mg and placebo	441 at 48 centers in 13 countries; 264 randomized to pooled tafamidis (176 to 80 mg and 88 to 20 mg) and 177 were randomized	See section 10b.

<sup>7</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

	safety, and tolerability of an oral daily dose of 20 mg or 80 mg tafamidis meglumine capsules compared to placebo.			to placebo	
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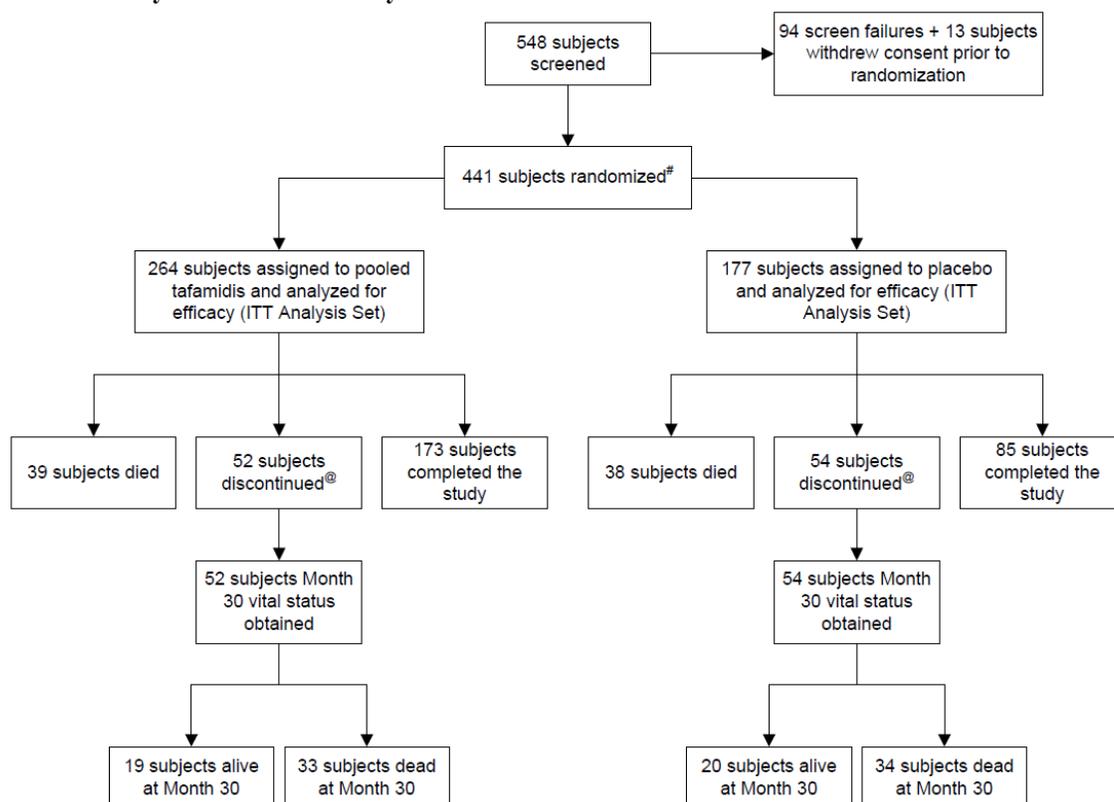
b. Include any additional relevant information. Consider the following in your response:

*Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*

- Approximately 1/4 of the patients enrolled had TTR of variant etiology and ~3/4 were wild-type (age related). Approximately 8% were NYHA Class I, ~60% were NYHA Class II and ~32% were NYHA Class III. Patients were randomized to Placebo, Tafamidis 20 mg and Tafamidis 80 mg in a 2:1:2 ratio.

Approximately 30% of subjects in the placebo arm and ~20% of subjects in the tafamidis arms discontinued from the study for TEAEs including transplant or cardiac mechanical assist device. See Figure 1 for precise number of subjects who discontinued.

**Figure 1: Disposition and Mortality Outcomes for Study B3461028**



# Subjects were randomized to placebo, tafamidis 20 mg, and tafamidis 80 mg in a 2:1:2 ratio.  
 @ Includes subjects that discontinued from the study for transplant or cardiac mechanical assist device.  
 Source: BTDR submission, p. 12.

The primary analysis uses a hierarchical combination applying the method of Finkelstein-Schoenfeld (F-S) to:

- All-cause mortality, and
- Frequency of CV-related hospitalizations over the duration of the trial, which was defined as the number of times a subject was hospitalized (i.e., admitted to a hospital) for CV-related morbidity.

The F-S method is based on the combination of all-cause mortality and CV-related hospitalization frequency and gives higher priority to mortality. It only uses CV-related hospitalization frequency when subjects are not able to be differentiated based on mortality. The primary analysis was a stratified test based on the two stratification factors (TTR genotype, and NYHA baseline classification). The results from the primary analysis are summarized below.

**Table 1: Primary Analysis using Finkelstein-Schoenfeld method**

<b>Primary Analysis</b>	<b>Pooled Tafamidis N=264</b>	<b>Placebo N=177</b>
Number (%) of Subjects Alive* at Month 30	186 (70.5)	101 (57.1)
Average CV-related Hospitalizations during 30 months (per patient); not adjusted for covariates	1.01	1.31
Average/Median CV-related Hospitalizations during 30 months (per patient per year); not adjusted for covariates	1.00/0.40	0.88/0.40
<b>p-value from F-S method</b>	0.0006	

\* Transplant involving heart and cardiac assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore, such subjects are not included in the count of “Number of Subjects Alive at Month 30” even if such subjects are alive based on 30 month vital status follow up assessment. (6 transplants/ cardiac assist devices in pooled Tafamidis group and 4 transplants/ cardiac assist devices in placebo group which were counted as deaths.)

Source: p. 13 of the sponsor’s BTDR submission

The p-value for the primary analysis was 0.0006 indicating a treatment effect favoring tafamidis. There is no statistically sound method for calculating hazard ratios of combined mortality and hospitalization rates. The percentage of subjects alive at Month 30 in the pooled tafamidis and placebo groups were 70.5 % and 57.1%, respectively. The hazard ratio for the all-cause mortality Cox-proportional hazard model was 0.7 (95% CI 0.51, 0.96) indicating a 30% reduction in risk of death in the pooled tafamidis group relative to the placebo group (p=0.026). The results of the composite primary endpoint in Study B3461028 were driven by the mortality results. The results for hospitalization were not quite as favorable as the mortality results, but the point estimate still favored tafamidis. Among subjects alive at month 30, the mean CV-related hospitalization frequencies per year were ~0.3 and ~0.5 respectively among the pooled tafamidis and placebo groups. The descriptive mean CV-related hospitalizations per patient were 1.01 and 1.31 among the pooled tafamidis and placebo groups, respectively, and the descriptive mean CV-related hospitalizations per patient per year were 1.00 and 0.88, respectively (not adjusted for covariates). The model based covariate-adjusted means for CV-related hospitalization frequency are presented in Table 2.

**Table 2: CV-related hospitalization frequency**

<b>Primary Analysis</b>	<b>Pooled Tafamidis</b>	<b>Placebo N=177</b>
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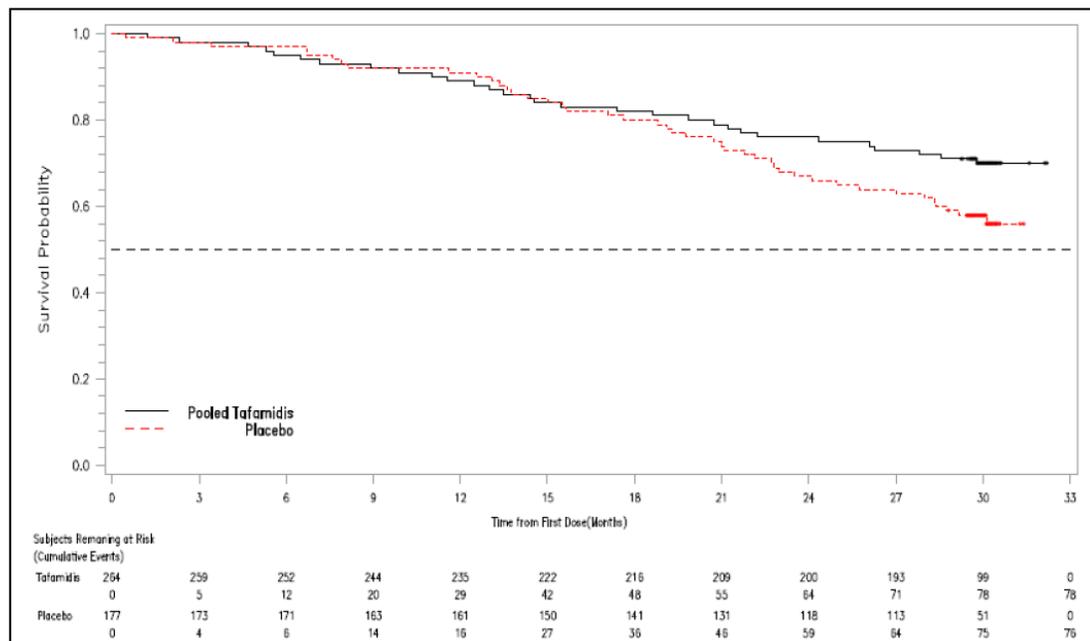
	<b>N=264</b>	
Total (%) Number of Subjects with CV-related hospitalizations	138 (52.3)	107 (60.5)
CV-related Hospitalizations per year*	0.65	0.73
Pooled Tafamidis vs. Placebo tx difference (relative risk ratio)	0.89	
<b>p-value from F-S method</b>	<b>0.27</b>	

\*This analysis was based on the annualized CV-related hospitalization frequency and a Poisson regression model. The model includes 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 and was adjusted for treatment duration.

**Source: p. 14 of the sponsor's BTDR submission**

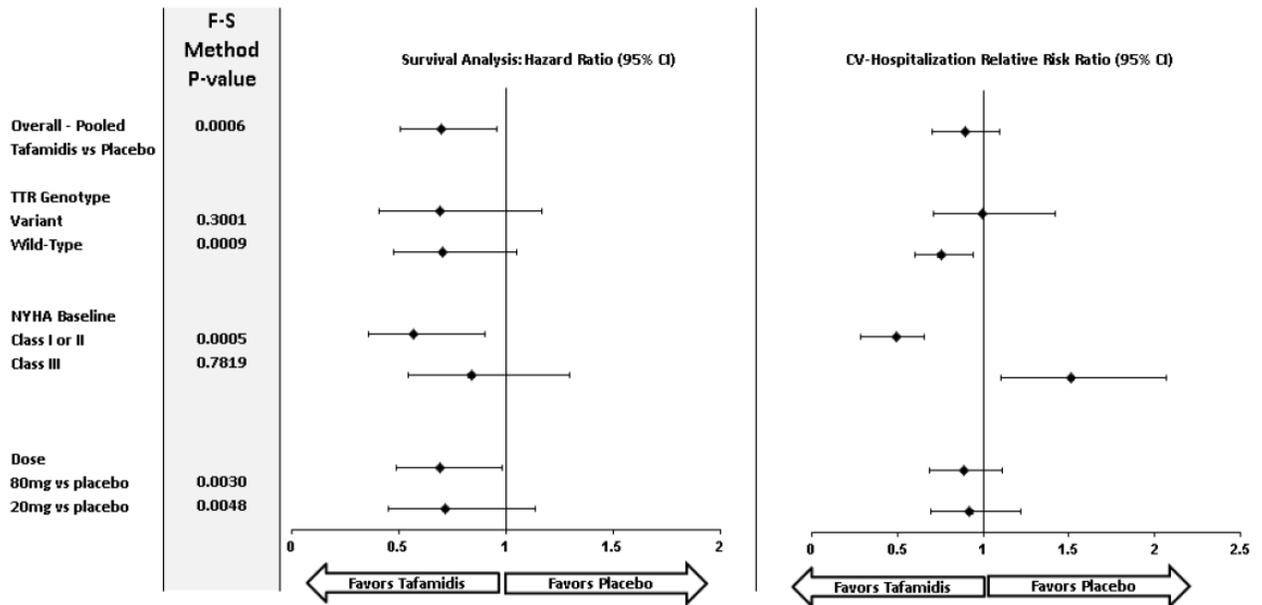
As shown in Figure 2, the separation in survival probability between the treatment groups began at ~ month 15 and widened throughout the rest of the observational period (~30 months).

**Figure 2: K-M Survival Curve (Counting Heart Transplant and Cardiac Assist Device Implantation as death)**



Source: BTDR submission, p. 13.

**Subgroup Findings:** There was a consistent directional survival benefit favoring tafamidis among important subgroups. See the forest plot below. The directional benefit was maintained for subgroups for CV hospitalization with the exception of NYHA III, a sicker population who would be expected to have a higher risk of hospitalization.



No multiplicity adjustment was specified for the components of the primary and the F-S subgroup analyses and their components.

Source: p. 15 of the sponsor’s BTDR submission

*Safety data:* The preliminary safety data showed that tafamidis was generally well tolerated in this population and no new safety signals were identified. The safety analysis set included 264 subjects in the pooled tafamidis group and 177 subjects in the placebo group. The proportion of subjects with SAEs and severe TEAEs was similar between the pooled tafamidis and placebo groups. The proportion of subjects discontinuing treatment due to TEAEs, either permanently or temporarily, was reduced in the pooled tafamidis group compared to placebo.

**11. Division’s recommendation and rationale (pre-MPC review):**

GRANT :

The rationale for granting BTDR is the success on the primary endpoint (combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared to placebo at 30 months) using the Finkelstein-Schoenfeld (F-S) method. The mortality benefit appears to have driven the results.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

**12. Division’s next steps and sponsor’s plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for

accelerated approval, recommending expanded access program): **A pre NDA meeting is scheduled on 21 May, 2018. The sponsor intends to submit an NDA to us in Q4 2018.**

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:** See the footnotes above.

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES  NO

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation   
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**Revised 3/20/18/M. Raggio**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MELANIE J BLANK  
05/14/2018

MARTIN ROSE  
05/14/2018

NORMAN L STOCKBRIDGE  
05/14/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 71880

**MEETING MINUTES**

Pfizer, Inc.  
Attention: Sharada Truder, PhD  
Director, Worldwide Regulatory Strategy  
500 Arcola Road  
Collegeville, PA 19426-3982

Dear Dr. Truder:

Please refer to your Investigational New Drug Application for tafamidis meglumine.

We also refer to the meeting between representatives of your firm and the FDA on March 28, 2012. The purpose of the meeting was to discuss the development of Tafamidis.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Russell Fortney, Regulatory Project Manager at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, MD  
Acting Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** End-of-Phase 2 Meeting

**Meeting Date:** March 28, 2012  
**Meeting Location:** FDA White Oak Campus

**Application Number:** IND 71880  
**Product Name:** Tafamidis meglumine  
**Indication:** Treatment of adult symptomatic transthyretin cardiomyopathy (TTR-CM)

**Sponsor/Applicant Name:** Pfizer

**Meeting Chair:** Ellis F. Unger  
**Meeting Recorder:** Russell Fortney

### FDA ATTENDEES

#### *Office of Drug Evaluation I*

Ellis F. Unger, MD Acting Director

#### *Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD Director  
Stephen Grant, MD Deputy Director  
Khin U, MD Medical Reviewer  
Al DeFelice, PhD Pharmacology Team Leader  
William Link, PhD Pharmacologist  
Russell Fortney Regulatory Project Manager

#### *Office of Clinical Pharmacology*

Sreedharan Sabarinath Clinical Pharmacology Reviewer

#### *Office of Biostatistics, Division of Biometrics I*

Jim Hung, PhD Director  
Jialu Zhang PhD Statistician

#### *Division of Neurology Products*

Ron Farkas, MD, PhD Medical Team Leader

#### *Division of Hematology Products*

Angelo De Claro, MD Medical Reviewer

#### *Office of Orphan Product Development*

Francesca Joseph, MD Medical Reviewer

#### *Rare Disease Program*

Gumei Liu, MD, PhD Commissioner's Fellow

### PFIZER ATTENDEES

Sharada Truter, PhD Director, Global Regulatory Lead  
Janske Aarts, MD Senior Director, Medicines Development Group

Rosonald Bell, PhD	Associate Research Fellow, Nonclinical Regulatory Strategy Lead
John Davis, PhD	Director, Drug Safety Team Lead
Clare Kahn, PhD	Vice President, Worldwide Regulatory Strategy, Specialty Care BU
Ilise Lombardo, MD	Senior Director, Medicines Development Group Lead
Susan Mather, MD	Senior Director, WSS Safety Surveillance & Risk Management
Robert Moller, PhD	Director, Clinician
Steve Riley, PharmD, PhD	Director, Clinical Pharmacology Lead
Jeff Schwartz, PhD	Senior Director, Statistics
Eric Watsky, MD	Executive Director, Global Clinical Lead
Iwona Jeske-Dupont, PhD	Executive Director – Regulatory Neurology Portfolio Lead

## BACKGROUND

Pfizer is developing tafamidis for use in the treatment of the rare disease symptomatic transthyretin (TTR) amyloid cardiomyopathy due to wild-type or variant TTR to slow progression of cardiomyopathy and to reduce the combination of mortality and cardiovascular hospitalization. Pfizer has been granted orphan drug designation for this indication. Pfizer is also developing tafamidis for use in TTR amyloid polyneuropathy; an NDA is currently under review in the Division Neurology Products for this indication. This meeting was requested to gain Agency feedback on Pfizer's phase 3 development program. Preliminary responses to the sponsor's questions were communicated to the sponsor prior to the meeting and are copied below followed by any additional discussion that took place during the meeting.

## DISCUSSION

The following questions were addressed:

1. Does the Agency agree that the overall tafamidis development program and the single pivotal placebo-controlled study in cardiomyopathy as presented will be sufficient to support licensure and the proposed indication?

**Preliminary Agency response:** Approvability depends on the specific results of your trial. If you submit an efficacy supplement to an approved NDA, a single trial successful at a 2-sided p-value of 0.05 would likely be adequate support, especially if the observed effects are consistent on both components of the primary endpoint. However, a NDA submission based on positive trial results driven entirely by an effect on hospitalization with a numerical imbalance in mortality favoring placebo is unlikely to result in approval. For further advice please consult our guidance *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*.

To increase the probability of your development program resulting in an approval, we strongly recommend you test more than one dose in your trial. The finding of a dose-response would provide additional evidence of effectiveness and would be useful for providing labeling instructions. Although 20 mg is a reasonable dose to test based on modeling, clinical results can and do sometimes diverge from models. In fact, the results of your confirmatory trial in FAP appear to be less robust than would have been anticipated based on your modeling. It seems that you have adequate safety data to test a dose four or five times higher than 20 mg (in fact you indicate that no significant safety concerns have been observed clinically and the NOAEL in nonclinical studies is at least two orders of magnitude higher than 20 mg). If you choose to test more than one dose, you may compare the pooled results of all doses versus placebo for the analysis of the primary endpoint, without adjustment.

**Additional discussion during meeting:** The sponsor noted that they are currently weighing this issue and are considering adding (b) (4) dose. Some concerns include potential tolerability issues, feasibility (the current formulation is a large 20-mg capsule), and potential protein binding issues at higher doses. The Agency reiterated the recommendation to include a higher dose, specifically a dose at least one-half log higher than 20 mg. A 60-mg dose (b) (4) will result in a clearer separation of exposures between the two dose-levels and facilitate exposure-response analyses. Dr. U noted that the sponsor has not found dose limiting toxicity.

There was also a discussion about the randomization scheme with two different doses of tafamidis plus placebo. The sponsor mentioned that they will consider whether the randomization should be 1:1:1 (placebo:20 mg:higher dose) with current sample size of approximately 250 patients, or include fewer subjects (~65) for the higher dose group, with an option to drop the higher dose group if there were any unexpected safety issues.

2. Does the Agency agree with the proposed single Phase 3 double-blind, randomized, 2-arm, placebo-controlled clinical study design for the proposed indication? Specifically:

A. Are the inclusion/exclusion criteria appropriate to define the study population for the proposed indication?

**Preliminary Agency response:** We have the following suggestions:

- Explain the rationale for excluding mutations other than V122I or L111M. While the V122I variant is the most common genetic variant causing cardiomyopathy and is estimated to be prevalent in 3.0% to 3.9% of African-Americans,<sup>1,2</sup> currently about 100 TTR variants are known<sup>3</sup> of which 32 genetic variants are present in the US, 25 being associated with cardiac disease. We note also that in a US community-based sample, approximately 30% of subjects aged 75 and older with congestive heart failure had cardiac deposits of wild-type TTR.<sup>4</sup>
- Indicate if patients who are on liver transplant lists are eligible to enroll.

**Additional discussion during meeting:** The sponsor clarified that they intend to include all cardiac-specific mutations.

The sponsor noted most patients are older and likely not eligible for liver or cardiac transplants, and thus they do not believe that transplant patients will impact the study. However, because the observation period is 30 months, some patients may go on a transplant list during the study. Therefore, their intention is to allow enrollment of patients on transplant lists. They also noted that patients with wild-type TTR would not be eligible for liver transplant.

B. Does the Agency agree that genetic mutations (eg, V122I, L111M) included in the protocol will be sufficient for an indication across all cardiac genetic variants?

**Preliminary Agency response:** The population of patients actually studied in the Phase 3 clinical trial will be described in the labeling. You need to enroll a variety of genetic variants to establish the general indication that you seek.

**Additional discussion during meeting:** No additional discussion.

<sup>1</sup> Jacobson DR, Pastore RD, Yaghoubian R, et al: Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in Black Americans. *N Engl J Med* 1997;336:466-473.

<sup>2</sup> Connors LH, Prokaeva T, Lim A, et al: Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J* 2009;158:607-614.

<sup>3</sup> Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants, 2003. *Amyloid*. 2003;10(3):160-84.

<sup>4</sup> Sultan AM, Edwards WD, Mohammed SF et al. Cardiac amyloid deposition is common in elderly patients with heart failure and preserved ejection fraction. *Circulation* 2010;122:A17926.

- C. Will the proposal to enroll patients with wild-type TTR-CM support a claim of efficacy in these patients?

**Preliminary Agency response:** This is possible depending on the results of your trial. We believe it unlikely that your trial will have sufficient power to show statistical significance in this subpopulation. If the observed efficacy in wild-type TTR-CM is similar to that of the overall population enrolled, it is likely the label will state that tafamdis is indicated for treatment of TTR-CM due to genetic variants of TTR and to wild-type TTR.

**Additional discussion during meeting:** No additional discussion.

- D. The proposed design and primary analysis is based on mortality and cardiovascular hospitalization days utilizing the methodology described by Finkelstein and Schoenfeld (1999). Is this approach acceptable and sufficient to support an efficacy claim?

**Preliminary Agency response:** You need to provide further details on how you assign the scores. For example, what scores do you assign if one patient dies on Day 9 and the other patient censors on Day 7? What scores do you assign if one patient dies on Day 9 without hospitalization and the other patient censors on Day 7 and have three days of hospitalization? What score do you assign if one patient censors on Day 9 and the other patient censors on Day 7? Does this method penalize for longer follow up? The detailed SAP should be submitted as early as possible.

It is possible that the event rates may be lower than expected and so we suggest that you consider performing an event-driven trial to avoid having your trial be underpowered. If you plan to increase the sample size based on the observed event rate, we recommend you prospectively document in your initial protocol and analytic plan a detailed algorithm to determine the size and timing of any adjustment to the sample size. It is also important to document how the blind will be maintained.

Mortality and clinical outcomes may vary with the type of TTR-CM (wild-type TTR-CM vs. genetic variant TTR-CM). Please indicate if subjects will be stratified for statistical analyses or for randomization.

If you plan to enroll patients who are already on a liver transplant list, they should be stratified prior to enrollment, and the “*time to discontinuation for liver transplantation*” may importantly impact the primary or secondary efficacy endpoints.

At the meeting, we would like to discuss “*time to liver transplantation*,” specifically, whether this reflects worsening of disease, or rather reflects the availability of a suitable donor organ.

Explain how discontinuations will be analyzed.

**Additional discussion during meeting:** The sponsor explained the Finkelstein and Schoenfeld scoring algorithm (see slides 6 – 7).

The Division asked why the sponsor chose hospital duration over time-to-hospitalization. The sponsor said they expect that as patients clinically deteriorate hospitalizations will become both more frequent and longer.

The Division stated that the sponsor is expected to ascertain the vital status of all subjects at the end of the trial and that failure to do so will jeopardize interpretability of the trial data.

The Division stated that if the sponsor intends to allow for an increase in sample size then a prespecified algorithm for doing so should be included in the protocol. This algorithm should clearly delineate when the decision(s) will be made, what information will be considered, and how the determination will be made.

- E. Does the Agency agree that the data from the single Phase 3 study (as proposed) will be adequate to support review of an NDA for this proposed indication?

**Preliminary Agency response:** See the response to question 1 above.

**Additional discussion during meeting:** No additional discussion.

3. Does the Agency agree that the primary and secondary variables in the proposed Phase 3 protocol would be sufficient to demonstrate that tafamidis slows the progression of disease?

**Preliminary Agency response:** We believe that the only proposed secondary endpoints that will be useful are 6MWT and the patient reported outcomes. Endpoints that are components or variants of the primary endpoint are useful as sensitivity analyses but should not included be as formal secondary endpoints that are part of an alpha conserving strategy because they will not result in additional claims. Similarly, endpoints that investigate the PD effects of drug administration may be described in the clinical pharmacology section of the PI but will not result in additional claims.

You should include in your analytic plan a multiple comparison method to control the overall type I error in testing secondary endpoints.

**Additional discussion during meeting:** The sponsor asked for clarification regarding what is needed to support a claim (b) (4).

The Agency said it was not prepared to discuss (b) (4) language at this time. However the

(b) (4)

4. Does the Agency agree that the safety data from the TTR-FAP program, and the safety data that will continue to be collected in the TTR-CM program, will be sufficient to support the safety database requirements for tafamidis as a treatment for the proposed orphan disease of TTR-CM?

**Preliminary Agency response:** We note that only 382 patients had been exposed to tafamidis thus far: 66 patients with TTR-CM and 316 patients with TTR-FAP (familial amyloid polyneuropathy). The proposed double-blind placebo-controlled Phase 3 study of 250 patients total will add 125 patients exposed to tafamidis, for a total exposure of 441 patients.

You should plan continuing long-term safety evaluations after the conduct of the Phase 3 clinical trial to increase the size of the safety database.

**Additional discussion during meeting:** No additional discussion.

5. Does the Division agree (b) (4)

(b) (4)

**Preliminary Agency response:** No. (b) (4)

(b) (4) You should conduct a TQT study per ICH E14 to determine if there is a significant signal for QTc prolongation prior to enrolling the first subject in your proposed trial. If you do not conduct a TQT (b) (4), you must (b) (4) include

extensive ECG monitoring for all subjects. Failure to do one or the other will likely result in a clinical hold.

**Additional discussion during meeting:** The sponsor noted that they will add extensive ECG monitoring (24-hour 12-lead ECGs) until such time as the TQT study is completed. Dr. Stockbridge stated the reason for intensive monitoring was for subject protection in phase 3, not for further characterizing the QT effect. He recommended obtaining 12-lead ECGs around  $T_{max}$  (and if tafamidis accumulates, also around “real”  $T_{max}$ ). The sponsor acknowledged their understanding of the need to evaluate the ECGs in real time.

6. Does the Agency agree that the completed nonclinical program supports the proposed clinical development plan for registration of tafamidis in TTR cardiac amyloidosis?

**Preliminary Agency response:** In general, the nonclinical program is adequate. However, the Division believes that carcinogenicity should be evaluated in two species, as is required for all chronically administered compounds. You have submitted a 2-year rat carcinogenicity study protocol, and the protocol was approved by the Executive Carcinogenicity Assessment Committee. We can discuss the timing of this second study during our face to face meeting.

**Additional discussion during meeting:** The sponsor noted that the second carcinogenicity study is planned to start in the second quarter of 2012.

#### Additional Preliminary Comments

- A. You should evaluate the potential for tafamidis to induce or inhibit transporters such as P-glycoproteins.
- B. We strongly recommend that you submit a Special Protocol Assessment for your trial well before you plan to initiate it so you can get detailed Agency feedback on the proposed design and analysis. You should include in this submission the protocol, statistical analytic plan, case report forms, site monitoring plans, and samples of the investigational products (both active and placebo). If adjudication of endpoints is to be performed by a clinical endpoint adjudication committee, provide a description of the procedure, charter and definitions used to adjudicate endpoints, and how blinding will be maintained during that process.

**Additional discussion during meeting:** The sponsor noted that they likely will not submit an SPA as they feel that they need to start the Phase III trial in the near future and they think they can adequately design the trial without the SPA. Dr. Stockbridge noted that an SPA is not a requirement. Dr. Grant reminded the sponsor that the conduct of the trial will be of critical importance and that the SPA process often allows the Agency to provide input on elements that insure the trial’s interpretability. Dr. Grant requested that the sponsor submit clinical trial material to their IND prior to initiating the trial.

The sponsor asked if a single trial is sufficient evidence to support approval [REDACTED] (b) (4) [REDACTED]. Dr. Unger said it is possible that a single trial could support approval and referred the sponsor to the Agency’s Guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

#### **ATTACHMENT: Sponsor’s Slides**

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELLIS F UNGER  
04/16/2012