Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Tafamidis and Tafamidis meglumine

## Proprietary Product Name: Vyndamax and Vyndaqel

## Sponsor: Pfizer Australia Pty Ltd

**September 2020**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

# Common abbreviations

| Abbreviation | Meaning |
|---|---|
| 6MWT | 6 minute walk test |
| ACM | Advisory Committee on Medicines |
| ACSS | Australia-Canada-Singapore-Switzerland |
| AE | Adverse event |
| ARTG | Australian Register of Therapeutic Goods |
| ATTR | Transthyretin amyloid |
| ATTR-CM | Transthyretin amyloid cardiomyopathy |
| ATTR-PN | Transthyretin amyloid polyneuropathy |
| AUC | Area under the concentration-time curve |
| BCRP | Breast cancer resistant protein |
| CER | Clinical evaluation report |
| CHMP | Committee for Medicinal Products for Human Use (European Union) |
| CI | Confidence interval |
| CL/F | Apparent clearance |
| CM | Cardiomyopathy |
| $C_{max}$ | Maximum observed plasma concentration |
| CMI | Consumer Medicines Information |
| CV | Cardiovascular |
| CYP3A4 | Cytochrome P450, family 3, subfamily A, polypeptide 4 |
| EAIR | Exposure-adjusted incidence rate |
| EMA | European Medicines Agency (European Union) |
| $E_{max}$ | Maximal response |

| Abbreviation | Meaning |
|---|---|
| EU | European Union |
| FDA | Food and Drug Administration (United States) |
| GVP | Good Pharmacovigilance Practice(s) |
| ICH | International Council for Harmonisation |
| IRD | Incidence rate difference |
| IRR | Incidence rate ratio |
| KCCQ-OS | Kansas City Cardiomyopathy Questionnaire – overall summary |
| LS | Least squares |
| LVEF | Left ventricular ejection fraction |
| MRI | Magnetic resonance imaging |
| NMT | Not more than |
| NT-proBNP | N-terminal prohormone of brain natriuretic peptide |
| NYHA | New York Heart Association |
| OAT | Organic anion transporter |
| PBRER | Periodic benefit-risk evaluation report |
| PD | Pharmacodynamics(s) |
| PF-06291826 | Drug development/sponsor code for tafamidis |
| PI | Product Information |
| PK | Pharmacokinetic(s) |
| PK-PD | Pharmacokinetic-pharmacodynamic |
| PSUR | Periodic safety update report |
| PT | Preferred Term |
| SAE | Serious adverse event |
| SY | Subject years of exposure |

| Abbreviation | Meaning |
|---|---|
| T4 | Thyroxine |
| TEAE | Treatment-emergent adverse event(s) |
| TESPO | Tafamidis Enhanced Surveillance Pregnancy Outcomes |
| $T_{max}$ | Time to reach maximum plasma concentration after drug administration |
| TSH | Thyroid-stimulating hormone |
| TTR | Transthyretin |
| TTRR | Tafamidis: transthyretin ratio |
| ULN | Upper limit of normal |
| US | United States |
| UTI | Urinary tract infection |
| vs | Versus |

# I. Introduction to product submission

## Submission details

### Vyndamax (Submission PM-2019-00391-1-3)

| | |
|---|---|
| *Type of submission:* | New chemical entity |
| *Decision:* | Approved |
| *Date of decision:* | 13 March 2020 |
| *Date of entry onto ARTG:* | 16 March 2020 |
| *ARTG number:* | 314813 |
| ▼ *Black Triangle Scheme:*[1] | Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia. |
| *Active ingredient:* | Tafamidis |
| *Product name:* | Vyndamax |
| *Sponsor's name and address:* | Pfizer Australia Pty Ltd<br>Level 17, 151 Clarence Street, Sydney NSW 2000 |
| *Dose form:* | Soft capsule |
| *Strength:* | 61 mg |
| *Container:* | Blister pack |
| *Pack size:* | 30 |
| *Approved therapeutic use:* | *Vyndamax is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).* |
| *Route of administration:* | Oral |
| *Dosage:* | Treatment should be initiated and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid cardiomyopathy |

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

(ATTR-CM).

The recommended dose of Vyndamax is 61 mg tafamidis orally once daily (see Section 5.1 Pharmacodynamic properties of the Product Information).

A single 61 mg Vyndamax (tafamidis) capsule is bioequivalent to 80 mg Vyndaqel (tafamidis meglumine) (administered as four 20 mg Vyndaqel capsules) and is not interchangeable on a per mg basis (see Section 5.1 Pharmacodynamic properties; and Section 5.2 Pharmacokinetic properties, of the Product Information).

No dose ranging studies have been undertaken.

For further information regarding dosage, refer to the Product Information.

**Vyndaqel (Submission PM-2019-01399-1-3)**

| | |
|---|---|
| *Type of submission:* | New chemical entity |
| *Decision*: | Approved |
| *Date of decision:* | 13 March 2020 |
| *Date of entry onto ARTG:* | 16 March 2020 |
| *ARTG number:* | 316241 |
| ▼ *Black Triangle Scheme:*[1] | Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia. |
| *Active ingredient:* | Tafamidis meglumine |
| *Product name:* | Vyndaqel |
| *Sponsor's name and address:* | Pfizer Australia Pty Ltd<br>Level 17, 151 Clarence Street, Sydney NSW 2000 |
| *Dose form:* | Soft capsule |
| *Strength:* | 20 mg |
| *Container:* | Blister pack |
| *Pack size:* | 30 |
| *Approved therapeutic use:* | *Vyndaqel is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).* |
| *Route of administration:* | Oral |

| | |
|---|---|
| *Dosage:* | Treatment should be initiated and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid cardiomyopathy (ATTR-CM).<br><br>The recommended dose of Vyndaqel is 80 mg tafamidis meglumine (administered as four 20 mg capsules) once daily.<br><br>A dose of 80 mg Vyndaqel (tafamidis meglumine) (administered as four 20 mg Vyndaqel capsules) is bioequivalent to a single 61 mg Vyndamax (tafamidis) capsule and is not interchangeable on a per mg basis (see Section 5.1 Pharmacodynamic properties; and Section 5.2 Pharmacokinetic properties, of the Product Information).<br><br>No dose ranging studies have been undertaken.<br><br>For further information regarding dosage, refer to the Product Information. |

## Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Vyndamax (tafamidis) 61 mg soft gelatin capsules for the following proposed indication:

> *Vyndamax is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy to reduce all-cause mortality and cardiovascular related hospitalisation.*

The sponsor also sought to register Vyndaqel (tafamidis meglumine) 20 mg soft gelatin capsules for the following proposed indication:

> *Vyndaqel is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy to reduce all-cause mortality and cardiovascular related hospitalisation.*

Transthyretin amyloid cardiomyopathy (also known as amyloid-transthyretin cardiomyopathy (ATTR-CM)) is a rare, fatal disorder characterised by the deposition of misfolded transthyretin (TTR) amyloid fibrils in the ventricular walls and progressive disruption in the ability of the heart to effectively pump blood through the circulatory system. Accumulation of amyloid leads to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure. ATTR-CM can occur by deposition of wild-type TTR protein (wild-type ATTR-CM was previously known as senile systemic amyloidosis or senile cardiac amyloidosis) or inherited as an autosomal dominant trait caused by a mutation in the *TTR* gene that predisposes to misfolding of transthyretin (also known as familial amyloid cardiomyopathy). The accumulation of amyloid is slow and ATTR-CM typically occurs in patients aged 60 years or older. A condition with a similar pathogenesis that affects the peripheral and autonomic nerves is known as transthyretin amyloid polyneuropathy (ATTR-PN).

There are currently no disease-modifying treatment options for ATTR-CM. Tafamidis is a novel substance in a new therapeutic class. It binds to and stabilises the TTR tetramer, a carrier protein for retinol and thyroxine, at the thyroxine binding sites. It aims to reduce

the breakdown of the tetramer into TTR monomers that can then undergo misfolding or unfolding, reducing formation of TTR amyloid and thereby reducing amyloid deposition.

This application was evaluated as part of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium;[2] with work-sharing between the TGA and the Health Sciences Authority (HSA) of Singapore.[3] Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

## Regulatory status

These products are considered new chemical entities for Australian regulatory purposes.

At the time the TGA considered these applications, a similar application had been approved in the United States (US) (approval 3 May 2019) for the following indication:

> *Vyndaqel and Vyndamax are indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.*

In Canada, Vyndaqel (tafamidis meglumine) was approved on 20 January 2020 for the following indication:

> *The treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.*

In Japan, Vyndaqel (tafamidis meglumine) was approved for the treatment of wild-type and variant forms of ATTR-CM on 26 March 2019.

A similar application was under consideration for the treatment of ATTR-CM in the European Union (EU), Singapore and Switzerland. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has given a positive opinion for tafamidis on 12 December 2019 for the following indication:

> *Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).*

On 23 January 2019, Vyndaqel (tafamadis) and Vyndamax (tafamidis meglumine) were granted a positive Orphan Designation;[4] by the TGA for the following indication:

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[2] The **ACSS Consortium** is a collaborative initiative of like-minded, medium-sized regulatory authorities between Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA) and the Swiss Agency for Therapeutic Products (Swissmedic). Regulatory authorities face very similar challenges, such as increasing workload and increasing complexities in the medicinal applications that are being regulated, thus contributing to increasing pressure on available resources. The purpose of the consortium is to build synergies and share knowledge amongst the regulatory authorities thereby enhancing efficiency of regulatory systems.
The ACSS Consortium consists of various projects that aim to help meet the challenges faced by regulatory authorities, including timely access to safe therapeutic products within a limited resource capacity. The ACSS uses a network of bilateral confidentiality agreements and Memoranda of Understanding to conduct their work.

[3] The **Health Sciences Authority (HSA)** is responsible for administering Singapore's national regulatory frameworks for pharmaceuticals, complementary medicines, medical devices, and other health products.

[4] **'Orphan drugs'** are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs, the TGA waives application and evaluation fees for prescription medicine

*For the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) due to wild type or variant transthyretin.*

### Product Information

The Product Information (PI) documents approved with the submission which is described in this AusPAR can be found as Attachment 1 and 2. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 1: Timeline for Submission PM-2019-00391-1-3 (Vyndamax) and Submission PM-2019-01399-1-3 (Vyndaqel)**

| Description | Date |
|---|---|
| Positive Designation (Orphan) | 23 January 2019 |
| Submission dossier accepted and first round evaluation commenced | 11 April 2019 |
| First round evaluation completed | 3 September 2019 |
| Sponsor provides responses on questions raised in first round evaluation | 1 November 2019 |
| Second round evaluation completed | 6 December 2019 |
| Delegate's Overall benefit-risk assessment and request for Advisory Committee advice | 7 January 2020 |
| Sponsor's pre-Advisory Committee response | 21 January 2020 |
| Advisory Committee on Medicines (ACM) meeting | (Early ACM advice: 1 to 2 August 2019.)<br>7 February 2020 |
| Registration decision (Outcome) | 13 March 2020 |
| Completion of administrative activities and | 16 March 2020 |

registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application, and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

| Description | Date |
|---|---|
| registration on the ARTG | |
| Number of working days from submission dossier acceptance to registration decision* | 187 |

*Statutory timeframe for standard applications is 255 working days

# III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section presents a TGA summary of wording used in the TGA's evaluation report, which discussed numerous aspects of the overseas evaluation reports and included some information that was considered commercial-in-confidence.

The following EU guidelines adopted by the TGA are relevant to this submission, besides the general guidelines:

- CPMP/EWP/235/95 Rev 1: Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure. Effective: 23 February 2001.

## Quality

Tafamidis 61 mg soft gelatin capsules use the free acid form of the drug substance while tafamidis meglumine 20 mg soft gelatin capsules use the meglumine form of the drug substance. Figures 1 and 2, shown below, present a chemical structure of tafamidis (free acid form) and tafamidis meglumine, respectively.

**Figure 1: Structural formula of tafamidis (free acid form)**

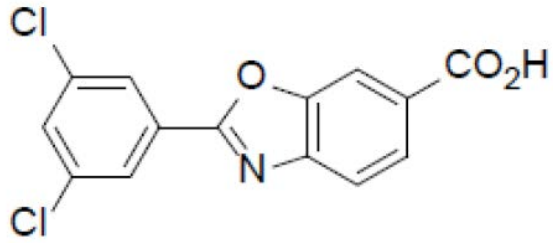
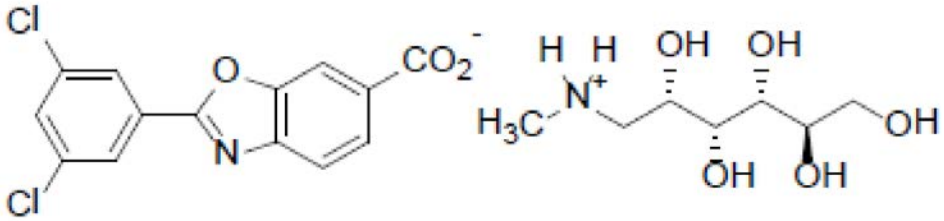



**Figure 2: Structural formula of tafamidis meglumine**




Both tafamidis (free acid form) and tafamidis meglumine are synthetic substances made in numerous steps and the starting materials and synthetic process are adequately

controlled. Data was provided to support a shelf life of 21 months and 24 months when stored below 25°C for tafamidis and tafamidis meglumine capsules, respectively.

### Pharmacokinetics and biopharmaceutics

Bioequivalence was demonstrated for a single dose of the marketing formulation of the 20 mg capsules to those used in the Phase III clinical efficacy study in the fasted state. Bioequivalence was also demonstrated for a single dose of the 61 mg tafamidis free acid capsules to 4 x 20 mg tafamidis meglumine capsules in the fasted state in the primary bioequivalence study. In another study, under fasted and fed conditions, each capsule formulation showed bioequivalence with respect to area under the plasma concentration time curve (AUC), however, they were bioinequivalent for the observed maximum plasma concentration ($C_{max}$) following drug administration (tafamidis meglumine-food reduces $C_{max}$ whereas tafamidis free acid-food increases $C_{max}$). This study also compared each capsule formulation under fasted and fed conditions but did not demonstrate bioequivalence.

### Conclusion

Following satisfactory resolution of outstanding issues post second round evaluation, approval was recommended from a quality perspective.

## Nonclinical

The nonclinical evaluator has no objections on nonclinical grounds to the registration of tafamidis and tafamidis meglumine for the proposed indications. There were no major deficiencies identified in the nonclinical dossier. The overall quality of the nonclinical dossier was generally high. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant.[5]

Primary pharmacology studies were limited to *in vitro* investigations due to the lack of an appropriately responsive animal model for ATTR-CM. Off-target effects by tafamidis on the $\delta_2$ opioid receptor and on cyclooxygenase 1/2 are not anticipated to have clinical relevance. Safety pharmacology did not reveal any specific hazards associated with tafamidis administration. There was limited central nervous system penetration of tafamidis. Tafamidis exhibited very high plasma protein binding (> 99%). Inhibition of breast cancer resistant protein (BCRP) and organic anion transporter (OAT) 1/3 by tafamidis is considered clinically relevant.

Target organs for toxicity were liver, kidney and lymphoid organs (spleen and thymus). Significant findings either occurred at moderate to high exposure margins or were species specific adaptive responses and are unlikely to be clinically relevant. Tafamidis was not genotoxic or carcinogenic. Adverse developmental effects (embryotoxicity, skeletal abnormalities, developmental delays, reduced viability) were observed at near, or below, the anticipated clinical exposure at the maximum recommended human dose. A pregnancy

[5] The principles of **Good Laboratory Practice (GLP)** define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.

Category D was therefore considered appropriate due to enhanced concerns over the risk to the human fetus.[6]

## Clinical

The clinical evaluator has recommended approval.

The clinical dossier includes 18 pharmacology studies, one pivotal clinical study and data from its ongoing long term extension, one uncontrolled study and data from its ongoing long term extension, one historical control study, three pharmacometric studies, six studies from the ATTR-PN development, three periodic benefit risk evaluation reports and 90 day and 120 day safety update reports.

Key features of the pivotal study overall design and primary endpoint were approved by the US Food and Drug Administration (FDA) and by the EMA. The FDA agreed that an application to register tafamidis for the ATTR-CM indication could rest on a single, strongly positive, well-designed pivotal study.

The following information is derived from the clinical evaluation report (CER). The CER included discussion regarding the definition of transthyretin (TTR) stabilisation (inclusion of this discussion is beyond the scope of this AusPAR).

### Early clinical advice

Tafamidis and tafamidis meglumine were considered by the Advisory Committee on Medicines (ACM);[7] in a pilot where early clinical advice was provided on the applications during the first round of clinical evaluation. This advice was sought to assist the TGA in identifying potential issues of clinical concern earlier that may require additional clinical evaluation and therefore could be addressed earlier in the evaluation process. Early advice was not sought on the other modules. The ACM minutes were provided to the sponsor and the questions and advice provided by the committee were responded to by the sponsor and have been considered in the second round clinical evaluation report.

The ACM considered and advised on the following requests for advice:

[6] **Australian Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

[7] The **Advisory Committee on Medicines (ACM)** provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

### *1. Whether there is any further clinical evaluation that the TGA should undertake or if the Committee has any comments on specific areas of the evaluation.*

*Efficacy*

The ACM considered the pivotal Study B3461028;[8] a multicentre, international, Phase III, double blind, placebo controlled, randomized study to evaluate the efficacy, safety, and tolerability of daily oral dosing of tafamidis meglumine 20 mg or 80 mg in comparison to placebo in subjects diagnosed with ATTR-CM. The ACM considered the study to be small for the cardiology context (n = 441). The ACM noted that the pivotal study is compliant with the relevant guideline.[9]

The ACM considered the primary endpoint, a combination endpoint of all-cause mortality and cardiovascular related hospitalisations, using Finkelstein-Schoenfeld analysis.[10] The ACM noted an overall reduction in mortality and hospitalisation in the pooled data set. Because deposition of amyloid is usually slow with the disease only appearing after decades, even in subjects with a predisposing mutation, it would be anticipated that the clinical benefit of tafamidis would also be slow to appear. The ACM noted that in the pivotal study (pooled data) patients had to survive 18 months without apparent benefit in order to achieve treatment benefit versus the placebo control. The ACM was of the view that this was a long period of treatment without benefit in symptomatic patients. Therefore, the ACM advised that early prediction of efficacy by use of a surrogate endpoint would be desirable. The ACM questioned if secondary endpoints such as the 6-Minute Walk Test (6MWT);[11] and the Kansas City Cardiomyopathy Questionnaire (KCCQ) – Overall Summary (OS);[12] were sufficiently predictive of clinical efficacy.

The ACM noted that the pooled efficacy data included subsets of patients classified as class I, II or III according to the New York Heart Association (NYHA).[13] Of these patients, 7 to

[8] ClinicalTrials.gov Identifier: NCT01994889; EudraCT Number: 2012-002465-35. Also known as the ATTR-ACT Clinical Trial

[9] EMA, Committee for Proprietary Medicinal Products (CPMP), (20 September 2017). Clinical investigation of medicinal products in the treatment of chronic heart failure. CPMP/EWP/235/95 Rev.2

[10] The **Finkelstein-Schoenfeld method** assesses pairs of patients, one from the active group and one from the placebo group, and evaluates which patient can be considered to have 'won', based on hierarchical criteria. In this study, the primary endpoint was based on which patient died first or, if this information was not applicable, it was based on which patient had the highest frequency of cardiovascular-related hospital admissions. Subjects who underwent cardiac transplantation or the insertion of a mechanical assist device were analysed as though they had died, but sensitivity analyses were also performed without treating transplantation or device insertion as deaths.

[11] The **6 minute walk test** is used to assess aerobic capacity and endurance, and measures the distance an individual can walk over a hard, flat surface in 6 minutes.

[12] The **Kansas City Cardiomyopathy Questionnaire (KCCQ)** is a 23-item self-administered questionnaire developed to independently measure the perception of health status in patients with heart failure. Overall Summary Score can be derived from the total symptom, physical function, social limitations and quality of life scores.

[13] The **New York Heart Association (NYHA) classification** places patients in one of four categories based on how much they are limited during physical activity. The following classification is used:
Class I - No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath);
Class II - Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath);
Class III - Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea; and
Class IV - Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

9% identified as class I. The ACM considered that class I patients would be asymptomatic and concluded that these patients would not normally be detected for treatment. The ACM advised that it is not known how the inclusion of class I patients in the pooled data has changed results. The ACM considered the subgroup analysis for sicker subjects with marked limitation of physical activity (class III) and advised that these patients experienced no benefit for survival with worsening of hospitalisation. The ACM noted that class III patients were a key target group in need of treatment.

The ACM considered that a comparison of hospitalisation rates in the two treatment groups is difficult to interpret and raised that a higher mean hospitalisation rate was observed in the pooled tafamidis group despite a lower median hospitalisation rate and a lower adjusted rate in the Poisson regression analysis. The ACM was of the view that this may reflect a small number of subjects in the pooled tafamidis group with a very high hospitalisation rate, which is consistent with subgroup analysis that identified higher cardiovascular -related hospitalisations in the tafamidis group for subjects with NYHA class III. The ACM requested that the secondary endpoint data (6MWT and quality of life questionnaire) be made available according to NYHA class at recruitment.

The ACM expressed concern that no efficacy studies had been performed with the proposed 61 mg free acid tafamidis capsule. The ACM noted that efficacy of the 61 mg capsule has been inferred from supporting studies conducted with tafamidis meglumine 80 mg capsules (4 x 20 mg), relying on pharmacokinetic data showing that tafamidis 61 mg capsules were bioequivalent to tafamidis meglumine 4 x 20 mg capsules. On a molar basis, each tafamidis meglumine 20 mg capsule contains 12.2 mg tafamidis, suggesting that 4 tafamidis meglumine 20 mg capsules would provide 48.8 mg of tafamidis. The ACM additionally expressed concern that no designated dose finding study was conducted for tafamidis and it is not known if the proposed dose is the most beneficial one. Furthermore, as there were low trough levels noted, it is unclear whether daily dosing is the most beneficial dose interval.

*Stabilisation*

The ACM advised that differences could exist in TTR tetramer stabilisation between samples from healthy patients and those from adult patients with wild type or hereditary transthyretin amyloid cardiomyopathy. The ACM noted that more than 120 different pathogenic variants causing amyloid cardiomyopathy have been reported in the *TTR* gene and that it is possible that some of these variants may not respond to treatment with tafamidis. Only a small number of known pathogenic variants are non-amyloidogenic. The ACM considered that these are more likely to be variants that result in loss of function of the transthyretin proteins. The most commonly known pathogenic transthyretin variant is Val50Met.[14]

The ACM noted that the stabilisation cut-off value for use in clinical studies was based on what was established in healthy volunteers. Percent stabilisation values falling above the 95% confidence interval (CI) of the placebo-treated healthy volunteers (32%) were determined to be 'stabilised'. In addition, the stabilisation data in healthy volunteers showed very large variation, making translation of data from healthy to diseased more difficult. The ACM was of the opinion that no data were provided in support of what level of stabilisation was actually achieved in the pivotal trial. Furthermore, there are no data that links a minimum level of stabilisation to an outcome. The ACM was of the view that

[14] Val50Met mutation = valine replaced by methionine at position 50 in the *TTR* gene

the term stabilisation appears to be simplistic for what is a state of flux, with significant variation in 'stabilised' versus 'non-stabilised' portions.

*In vivo effect of tafamidis*

The ACM considered the statistical nature of the criterion for improvement of stabilisation and agreed that the definition of stabilisation is arbitrary from a clinical perspective. The ACM noted that 100% stabilisation referred to a doubling in the fraction of tetramer that remains intact following urea denaturation (for example, an improvement from 10 to 20% would be reflected as a 100% stabilisation) due to the normalisation that was applied. In addition, the ACM noted that it was not clear how many patients were part of this analysis.

The ACM was of the view that no data were presented to establish if the achieved levels of stabilisation are clinically important. The ACM considered that the sponsor has not directly demonstrated that tafamidis actually reduces deposition of amyloid in the ventricular walls of patients with ATTR-CM. The primary pharmacodynamics effect is that tafamidis binding inhibits TTR dissociation and stabilises TTR in the folded state, slowing the rate limiting step in the formation of amyloid. The ACM agreed that it was plausible that this could lead to reduction in the tissue deposition of amyloid, but this was not examined, or identified by the supporting studies.

The ACM noted that the most important secondary pharmacodynamics effects of tafamidis in ATTR-CM patients would consist of cardiac remodelling or changes in the amyloid content of the ventricular wall, as assessed with imaging or post-mortem studies, or potentially changes to the diastolic behaviour of the ventricle observed during echocardiography. The ACM expressed surprise that no data on echocardiogram or cardiac magnetic resonance imaging (MRI) parameters were provided by the sponsor, although these studies were mentioned. The ACM was of the view that further clarification as to what the imaging studies showed, and whether gadolinium was used in the cardiac MRI studies would be beneficial, and in particular, whether there was a change in the amount of late gadolinium enhancement on therapy?

The ACM noted that only minimal pharmacodynamic data were collected in the submitted studies and also noted the absence of robust data showing effects on rate of deterioration or rate of progression. The pivotal efficacy study included some echocardiographic endpoints, but no strong evidence was provided on changes or reduced disease progression in the left ventricular wall of ATTR-CM subjects in response to tafamidis. The ACM was of the view that it would be important to determine if the therapy is purely preventative (that is, halts progression), an active treatment (that is reverses disease by reversing amyloid deposition) or both.

*Statistical considerations*

The ACM observed that the stabilisation cut-off value for use in clinical studies was based on percent stabilization values falling above the 95% CI of the placebo-treated healthy volunteers. The ACM noted that 95% CI is based on the further assumption that the data set has a normal distribution (unless a large sample was available). The ACM considered that the data set may not follow a normal distribution and this should be pursued as an evaluation question.

The ACM noted the Finkelstein-Schoenfeld method allows analysis of data in a joint structure over time and could be modified to look at different NYHA classes. The ACM advised that this method has been used from time to time in clinical research papers but is little used outside that field. The test answers the question of whether the treatment

works and cannot address how a treatment works. This method does not assume normal distribution.

The ACM further noted that for the long term extension Study B3461045 the sponsor has replaced the Finkelstein-Schoenfeld method with Cox regression and Kaplan-Meier curves. The ACM was of the view that the reason why the method of analysis has been changed has not been made clear and suggested that this information should be sought from the sponsor.

*Safety*

The ACM noted that in the pivotal study cohort (Study B3461028) there was a very high percentage (> 98.2%) of treatment emergent adverse events (TEAE) in all groups including tafamidis meglumine 20 mg, tafamidis meglumine 80 mg and placebo groups, since all patients had cardiomyopathy. The ACM noted that no signal of harm was detected in tafamidis meglumine dosed patients.

***2. Whether the Committee has advice on additional questions that the sponsor should address?***

The ACM suggested that additional questions to the sponsor could include requests for:

- Provision of primary analysis for cardiovascular related mortality and hospitalisation following separation of the pooled data set into sub-sets by NYHA class to address whether benefits existed across all NYHA classes. Data analysis excluding results from NYHA class I patients would also be of value.
- Subgroup analysis on the key secondary endpoints 6MWT and KCCQ-OS by NYHA class, to determine if these might be useful early clinical predictors of efficacy.
- Further dose finding studies and data for analysis that includes the specific formulation and dose being proposed for registration.
- Further information on the United States (US) Food and Drug Administration (FDA) concerns regarding pharmacodynamics as outlined when they considered the neuropathy indication, and how these were addressed.
- Further information on the proposed diagnostic criteria for the diagnosis of ATTR-CM, including clarification on whether cardiac biopsy will be a pre-requisite for diagnosis, and whether data and analysis on echocardiogram or cardiac MRI parameters are available.
- Further data to address the issue of whether tafamidis reduces amyloid deposition in the heart or causes regression in amyloid deposition volume, that is, whether it acts as a preventative or active treatment (or both). How will this be measured in clinical practice?
- Further analysis of whether the data set supporting the stabilisation cut-off value for use in clinical studies follows a normal distribution**.**
- Further explanation of the reason why the method of analysis has been changed for the long term extension Study B3461045 (from Finkelstein-Schoenfeld method to Cox regression and Kaplan-Meier curves).

***3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to the evaluation of this submission***

The ACM was of the opinion that the PI would need to capture the following information, based on the information provided in the clinical evaluation report (draft, first round):

- This medication is assumed to work by reducing the dissociation of tetramers.
- No studies have been undertaken to establish a relationship between the above and an effect on reduction of amyloid deposition in the heart.
- No dose ranging studies have been undertaken, so it is unknown whether the proposed dose is the most beneficial. The pivotal study did not use one of the proposed formulations or doses.
- The study recruited some subjects that classified as NYHA class I and were expected to be asymptomatic.
- The diagnostic criteria used to identify subjects in the clinical trial.
- There was no clear demonstration of benefit for the most symptomatic individuals classified as NYHA class III.

**Pharmacology**

The pharmacology studies included 18 studies (17 primarily pharmacokinetic (PK) and some with pharmacodynamics (PD) data and a thorough QT study;[15] (the Phase I, Study B3461031;[16])). Some of the key PK conclusions are:

- A single dose of tafamidis meglumine 80 mg (4 x 20 mg) capsules, showed a $T_{max}$ between 1.5 and 3 hours, with a $C_{max}$ that is roughly proportional to dose and an elimination half-life has been estimated to be between 41.5 and 52.2 hours. With multiple once-daily doses, steady state is achieved within approximately 11 to 15 days.
- After oral administration of the commercial tafamidis 61 mg capsule, peak concentrations occur within approximately four hours.
- Volume of distribution was approximately 16 L for tafamidis meglumine and 18.5 L for tafamidis. Tafamidis is extensively protein bound (> 99%) in plasma.
- The bioavailability of 61 mg tafamidis free acid capsule appears to be equivalent to tafamidis meglumine 80 mg (given as four 20 mg capsules).
- Tafamidis is largely excreted unchanged in the faeces, but it also undergoes glucuronidation and a small component is excreted as a glucuronide in the urine.
- Food has minor effects on the PK of tafamidis, leading to an altered rate of absorption. Tafamidis can be taken with or without food.
- Exposure appears to be reduced in hepatic impairment (moderate group more than mild group), but the sponsor proposes that this is offset by lower TTR levels in such subjects, such that no overall dose adjustment is necessary. PK in severe hepatic impairment were not assessed.
- No study specifically assessed the effect of renal impairment on the PK of tafamidis.

[15] The **QT interval** is the time taken from the start of the Q-wave to the end of the corresponding T-wave of the cardiac cycle, roughly corresponding to the onset of cardiac ventricular contraction to the end of subsequent ventricular contraction. A **QT study** is designed to evaluate the effect of a drug on the QT interval and the potential arrhythmia liability of a drug.
[16] Study B3461031: A study to determine any effect of tafamidis on electrocardiographic intervals, specifically the rate corrected QT interval (QTc). ClinicalTrials.gov Identifier: NCT01775761.

- Apparent clearance (CL/F) was 14.5% lower in older subjects (age ≥ 65) compared to younger subjects (age < 65) but no dose adjustment is proposed.
- Weight was a significant covariate in the sponsor's population PK analysis, but the effect was minor, and weight-based dosing does not appear to be necessary.
- One potential drug interaction was assessed with midazolam as a probe for cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4) induction showing no significant impact on the PK of midazolam.
- Tafamidis does not appear to have a clinically significant induction or inhibition effect on hepatic enzymes. It may inhibit the efflux transporter, breast cancer resistant protein (BCRP), and so it may increase systemic exposure to substrates of this transporter (for example, methotrexate, rosuvastatin and imatinib). Dose adjustment might be appropriate for substrates with a narrow therapeutic index, such as methotrexate.

Some of the key conclusions on PD are:

- Tafamidis is intended to bind to transthyretin, stabilising it in its tetrameric form, and thereby inhibiting the formation of amyloid.
- Tafamidis has been shown to increase TTR 'stabilisation', quantified by the sponsor as the proportion of TTR that survives denaturation in plasma during *in vitro* exposure to high concentrations of urea for 48 hours. The *in vitro* stabilisation effect appears to depend on the tafamidis: TTR molar ratio (TTRR), with stabilisation improving at progressively higher TTRR, up to a plateau. The sponsor's PD analysis suggested that the stabilising effect of tafamidis varies across different populations, with less percentage stabilisation in subjects with clinical amyloidosis, and in subjects with mutated TTR. Two genotypes in three subjects in the pivotal study were associated with apparent resistance to the *in vitro* stabilisation effects of tafamidis.[17]
- Healthy volunteers generally showed that percentage *in vitro* TTR stabilisation declined towards the end of the dosing interval.
- The sponsor's exposure-response model, which sought to characterise the relationship between % TTR stabilisation and TTRR, suggested that the maximum PD response (maximum effect; $E_{max}$) declines over time. At steady-state, substantial (but not maximal) stabilisation is likely to be present through most of the dose cycle, with relatively minor loss of stabilisation towards the end of the dose interval.

[17] Sponsor clarification: In their response to a request for additional information, the sponsor has asked for the following additional information about these three subjects to be included. 'However, in Study B3461028 there were 2 genotypes (Pro24Ser and Val20Ile) in 3 subjects for whom stabilization was not calculable at any time point during the 30 month study.
All three patients were NYHA Class II at Baseline and randomized to the tafamidis meglumine 80 mg arm. A model-based TTE analysis identified 5 baseline characteristics, including baseline left ventricle ejection fraction (LVEF) and N terminal pro-brain natriuretic peptide level (NT-proBNP), as important predictors of survival. Overall, based on those 5 baseline characteristics, the predicted survival probability for all 3 patients would have been rather high, above 0.714, had they been assigned to placebo. Since all were in the tafamidis meglumine 80 mg arm, their predicted survival probabilities reached > 0.835. However, for these 3 patients, none of the individual characteristics alone were predictive of outcome, perhaps with the exception of LVEF. A subject died at 604 days and had a baseline LVEF that was very low (25%), whereas the other two had baseline LVEFs of 70 and 79% and survived the 30 month duration of the trial.'

- Tafamidis was shown to have no important effects on the QT interval;[15] of the electrocardiogram when administered as a supratherapeutic dose of tafamidis meglumine 400 mg.
- A major deficiency in the PD characterisation of tafamidis was the lack of any clear demonstration of reduced amyloid formation in tafamidis recipients.
- No strong evidence was produced showing changes or reduced disease progression in the left ventricular wall of ATTR-CM subjects in response to tafamidis.

A separate pharmacometric evaluation was undertaken of the three pharmacometric studies and there were no outstanding issues. Expert advice was also obtained from the Pharmacometrics Working Group formed by the TGA. The pharmacometric evaluator's initial conclusions were:

- The development of the population PK model described in the Study PMAR-EQDD-B346a-Other-452 was well described, and the parameterisation well justified. The final model in Study PMAR-EQDD-B346a-Other-452 population PK modelling of PF-06291826 (tafamidis) was replicated using NONMEM version 7.4 and PSN version 4.7.0. The model replicated easily with minimal differences in parameters. Any differences are considered to reflect different versions of the software and systems used and are not of concern. The overlay of observed data for model verification showed the model provided suitable estimates of the data.
- Based on population PK results, the apparent oral clearance of tafamidis meglumine is 0.228 L/h (0.263 L/h for tafamidis) and the population mean half-life is approximately 49 hours.
- The pharmacokinetic-pharmacodynamic (PK-PD) modelling of TTR stabilisation showed a greater effect with 80 mg than 20 mg dosing and an overall time dependent decrease in effect.
- The exposure response analysis predicted poorer outcomes in patients with variant type compared with wild-type ATTR. It also predicted poorer outcomes in patients with higher urea, increased N-terminal pro B-type natriuretic peptide (NT-proBNP);[18] and left ventricular ejection fraction (LVEF), lower baseline 6MWT (which may reflect the functional effects of the reduced LVEF) and elevated troponin. While there are interrelationships between most of these variables, patients with features consistent with more advanced heart failure are predicted to have less favourable outcomes, based on the modelling.

The pharmacometric evaluator's final conclusion noted the sponsor has clarified a number of issues in the responses to questions. The evaluator considered the sponsor had provided sufficient clarification regarding its dosing recommendations in moderate hepatic impairment.

[18] **N-terminal pro B-type natriuretic peptide (NT-proBNP):** NT-proBNP is a prohormone with a 76 amino acid N-terminal inactive protein that is cleaved from the molecule to release brain natriuretic peptide. NT-proBNP levels in the blood are used for screening, diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure, as both markers are typically higher in patients with worse outcome. The plasma concentrations of both BNP and NT-proBNP are also typically increased in patients with asymptomatic or symptomatic left ventricular dysfunction (reduced LVEF) and is associated with coronary artery disease and myocardial ischemia.

## Efficacy

The sponsor did not perform Phase II dose-ranging studies prior to choosing 80 mg daily of tafamidis meglumine (61 mg daily of tafamidis free acid) as the preferred dose. The 80 mg daily dose was based on TTR stabilisation data from multiple Phase I PK/PD studies. A 20 mg daily dose was also included in the single pivotal study to provide comparative dose-related efficacy data, and to assess the possibility of dose-related safety or tolerability issues.

### *Study B3461028*

Study B3461028 was a multicentre, multinational, Phase III, randomised, double blind, parallel group, placebo controlled study that compared the efficacy and safety of tafamidis meglumine (20 mg/day or 80 mg/day) versus placebo (in addition to standard care for their cardiac failure), in 441 patients for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) for 30 months. The primary efficacy endpoint was a combination of all-cause mortality and cardiovascular-related hospitalisations, using the methodology of Finkelstein and Schoenfeld for the pooled tafamidis group versus placebo. Subjects were stratified by *TTR* genotype (variant versus wild-type) and by baseline NYHA classification. The key secondary endpoints were the 6MWT, and the KCCQ–OS. A pre-specified hierarchical order for testing the primary and key secondary endpoints was used. Other endpoints were assessed but no correction for multiplicity was used, including for efficacy of individual dose groups. Patients included in the study were adults with ATTR-CM, NYHA class I to III, either variant or wild type *TTR* genotypes with a documented biopsy to determine the presence of amyloid (for example, fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac) and demonstration of TTR precursor protein. Subjects with NYHA class IV were excluded. Study completion was relatively low at 58.5% across all groups which partly reflects the high mortality of the condition (17.5% death and 24% discontinued for other reasons). Baseline demographic data were acceptably matched across groups with pooled tafamidis mean age of 74.5 years and 91% male. Baseline disease characteristics in the pooled tafamidis group were: 9.1% NYHA class I, 61.4% class II, 29.5% class III, 76.1% wild type *TTR* genotype and 23.9% variant *TTR* genotype.

*Results*

The primary efficacy endpoint demonstrated a statistically and clinically significant effect for the pooled tafamidis group compared to placebo ($p = 0.0006$), with a reduction in the hierarchical combination of all-cause mortality and frequency of cardiovascular (CV) related hospitalisations (see Table 2).

**Table 2: Study B3461028 Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of cardiovascular-related hospitalisations by pooled active treatment (intent to treat analysis set)**

| | Pooled Tafamidis (N=264) | Placebo (N=177) |
|---|---|---|
| Number of subjects alive, n (%) | 186 (70.5) | 101 (57.1) |
| Average CV-related hospitalizations during 30 months (per year) among those alive at Month 30[a] | 0.297 | 0.455 |
| p-value from Finkelstein-Schoenfeld method[b] | 0.0006 | |

a. CV-related hospitalizations per year is calculated as (Subject's number of CV related hospitalizations) / (duration on study in years).
b. The Finkelstein-Schoenfeld test is a hierarchical comparison of mortality and cv-hospitalization. Each subject in the clinical study is compared with every other subject within each stratum in a pairwise manner (4 stratum based on NYHA Class and TTR genotype). Subjects, who discontinued for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death stratum in a pairwise manner. The primary comparison tests if at least 1 and possibly both all-cause mortality and frequency of CV related hospitalizations are different between the tafamidis and placebo treatment groups.

CV = cardiovascular; N = total number of subjects; n = number of subjects.

The proportions of patients contributing to each part of this combined endpoint are summarised in Table 3, as follows.

**Table 3: Study B3461028 Summary of mortality and hospitalisations for efficacy analysis (intent to treat analysis set)**

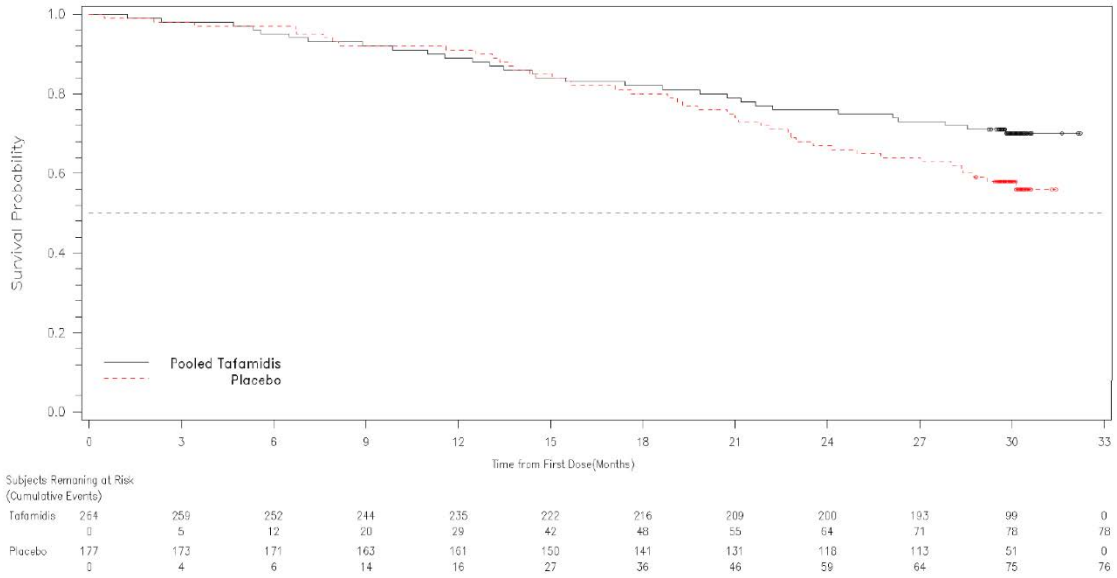
| | Tafamidis 20 mg (N=88) n (%) | Tafamidis 80 mg (N=176) n (%) | Pooled Tafamidis (N=264) n (%) | Placebo (N=177) n (%) |
|---|---|---|---|---|
| All Subjects: | | | | |
| Total Deaths[a] | 23 (26.1) | 49 (27.8) | 72 (27.3) | 72 (40.7) |
| CV-related | 17 (19.3) | 36 (20.5) | 53 (20.1) | 50 (28.2)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

Abbreviations: CV = cardiovascular; ITT = intent-to-treat; N = total number of subjects; n = number of subjects.
Note: CV-related as determined by Adjudication Committee.
a. Deaths (Notice of Death case report form recorded) up to 30 months post randomization are counted.
b. Hospitalizations where the subject is admitted to a hospital over the duration of the trial are included in this analysis; any hospitalizations prior to randomization date are not included. A subject may be counted for each category of hospitalization that applies.
c. Heart Transplants include heart and heart-combo transplantations.

The percentage of subjects still alive at Month 30 in the pooled tafamidis and placebo groups was 70.5% and 57.1%, respectively, which represents an absolute mortality difference of 13.4%, implying the number needed to treat = 7.5 over 30 months. The hazard ratio for all-cause mortality using the Cox proportional hazards model was estimated to be 0.698 (95% CI 0.508, 0.958) favouring tafamidis. The Kaplan-Meier plot

shows that the survival curves began to separate after about 18 months of treatment (see Figure 3).

**Figure 3: Study B3461028 Kaplan-Meier plot of time to event all-cause mortality; pooled active treatment (intent to treat)**




The frequency of CV related hospitalisations per year, adjusted for baseline factors, was 0.4750 and 0.7025 for the pooled tafamidis and placebo groups, respectively. The relative risk ratio between the pooled tafamidis and placebo groups was 0.6761 (95% CI 0.5792, 0.7776), suggesting a relative 32.39% reduction in the risk of CV related hospitalisation in the tafamidis group relative to placebo. However, a direct comparison of hospitalisation rates in the two treatment groups was difficult to interpret.

For key secondary endpoints, the change in the 6MWT at Month 30 showed a statistically significant treatment effect in favour of tafamidis with a least squares (LS) of the mean between-group difference of 75.68 metres (95% CI: 57.56, 93.80, $p < 0.0001$) from a Baseline of 351 to 353 metres across groups, with a significant difference between groups first observed at 6 months. The KCCQ-OS score at Month 30 showed a statistically significant treatment effect favouring tafamidis with a LS-mean difference from placebo of 13.65 (95% CI: 9.48, 17.83, $p < 0.0001$) from a Baseline score of 67 to 66 across groups, with a significant difference between the groups first observed at 6 months.

Other secondary endpoints showed a significant benefit for tafamidis. CV related mortality for the pooled tafamidis and placebo groups was 24.2% and 35.6% subjects, respectively, and the hazard ratio from the Cox-proportional hazard model was 0.691 (95% CI 0.488, 0.980), suggesting a 30.9% relative reduction in the risk of CV related death in the pooled tafamidis group, compared to the placebo group ($p = 0.0383$) and an absolute reduction of 11.4%. TTR stabilisation at Month 1, based on a pre-dose sample, showed a significantly greater proportion of subjects in the pooled tafamidis group demonstrated TTR stabilisation than was observed in the placebo group (86.1% versus 3.5% of subjects, $p < 0.0001$).

Other exploratory endpoints were discussed in the clinical evaluation report for these submissions, but are beyond the scope of this AusPAR.

The study was not powered for individual dose comparisons with placebo or between doses. For NT-proBNP, a larger mean difference from placebo was observed in the change from Baseline to Month 30 for the 80 mg group compared to the 20 mg group.

The pivotal study was not specifically powered for subgroup analyses, but the sponsor provided separate analyses for subgroups defined according to their NYHA classification and their *TTR* genotype. Some commentary is given below [further discussion and other endpoints were discussed in the clinical evaluation report but are beyond the scope of this AusPAR].

- By *TTR* genotype, wild-type patients treated with tafamidis had a significantly reduced combination of all-cause mortality and frequency of CV related hospitalisation relative to placebo (p = 0.0009). By contrast, a significant treatment effect of tafamidis was not observed between pooled tafamidis and placebo subjects for variant TTR (p = 0.3001), however this may be due to reduced power. Of note in subjects with variant type, mortality was lower in tafamidis recipients, but the frequency of hospitalisation was higher, relative to placebo. TTR stabilisation also varied by genotype with variant type showing reduced stabilisation compared to wild type (for example, 58.9% versus 94.2% for variant versus wild type after one month of treatment on tafamidis). For two particular variant *TTR* genotypes (*Pro24Ser* and *Val20Ile*);[19] present in 3 subjects, all on 80 mg tafamidis, TTR stabilisation was not demonstrated at any time point throughout the study with one patient who had LVEF of 25% at Baseline and died at Day 604 and the other two patients had LVEF of 70% and 79% at Baseline and completed the study.
- By NYHA classification, the combined endpoint of all-cause mortality and frequency of CV related hospitalisations showed a significant treatment effect for tafamidis compared to placebo in patients with baseline NYHA class I/II (p = 0.0005), but not for NYHA class III (p = 0.7819). All-cause mortality favoured tafamidis regardless of NYHA class but this was not statistically significant for NYHA class III patients. CV related hospitalisation showed a significant benefit for tafamidis in NYHA class I/II combined but not for NYHA Class III patients who demonstrated significantly higher CV related hospitalisation on tafamidis than placebo (risk ratio = 1.41114, p = 0.0231). The inclusion of class I subjects did not appear to excessively influence the primary analysis.

### *Study B3461045*

Study B3461045;[20] (enrolled n = 252 at data cut-off) is an ongoing safety extension study to the pivotal study, Study 3461028, for up to 60 months. Following a protocol amendment, blinding was removed and patients receiving 20 mg or 80 mg were to be assigned to the 61 mg tafamidis. New patients could also be enrolled on 61 mg tafamidis. No study report was submitted but some interim results were presented and werediscussed in the clinical evaluation report [discussion is beyond the scope of this AusPAR]. In a *post-hoc* comparison of all-cause mortality in the extension study, for the 20 mg and 80 mg doses, the hazard ratio was 0.8976 (95% CI: 0.5711, 1.4108), indicating a 10.2% reduction in risk of death in patients receiving 80 mg relative to patients receiving 20 mg (p = 0.6395) but this was not statistically significant.

[19] *Pro24Ser* = proline replaced by serine at position 24; and *Val20Ile* = valine replaced by isoleucine at position 20.
[20] Study B3461045: Long-term safety of tafamidis in subjects with transthyretin cardiomyopathy; ClinicalTrials.gov Identifier: NCT02791230; EudraCT Number: 2016-000868-42.

Other supportive studies were discussed in the clinical evaluation report [discussion is beyond the scope of this AusPAR].

**Safety**

Four studies (Studies B3461028, B3461045, B3461025 and B3461026) in ATTR-CM were pooled to provide an integrated safety set (n = 377) but the pivotal study, Study B3461028, provides the main data source along with some data from its long term extension. No important safety issues were identified in the Phase I study program (n = 348), but most of these studies involved single doses or a very short duration of treatment. Safety data were also provided from the ATTR-PN program (n = 137), post-market experience and the observational registry (n = 785). The following is from the pivotal study, Study B3461028, unless noted otherwise, with other data in the clinical evaluation report, which are beyond the scope of this AusPAR.

Exposure was a mean 24 months in the pooled tafamidis meglumine group with 183 subjects exposed for 24 to 36 months in the pooled group (for tafamidis 80 mg, 119 were exposed for 24 to 36 months). TEAEs were similarly high across all three treatment groups (98.9%, 98.3%, and 98.9% in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively). The safety profile was broadly similar between tafamidis and placebo. The most common (≥ 10%) severe events were cardiac failure (reported in 14.1%, 12.5%, and 11.9% of the placebo, tafamidis 20 mg and tafamidis 80 mg treatment groups, respectively), and congestive cardiac failure (12.4%, 14.8%, and 8.5%, respectively). Among TEAEs that were common (≥ 10% in at least one group), the only TEAEs with an incidence in the pooled tafamidis group more than 2% higher than in the placebo group were asthenia and pneumonia. TEAEs with an incidence among tafamidis recipients that was at least twice that observed in placebo recipients and which were reported by at least 4 patients included cataract, flatulence, cystitis, sinusitis, arthritis, myalgia, asthenia, balance disorder, hyperhidrosis, and skin ulcer. The evaluator considered there was no overall pattern to suggest a causal relation with tafamidis treatment. Including the extension study showed some TEAEs (atrial fibrillation, acute cardiac failure, diarrhoea, bronchitis, pneumonia, and pain in the extremities) with a higher incidence in the 80 mg dose group than in the 20 mg dose group. Others were less with 80 mg, for example, congestive cardiac failure and cardiac failure in general. In the pivotal ATTR-PN Study Fx-005, TEAEs that occurred more commonly in tafamidis than in placebo included diarrhoea (tafamidis 26% versus placebo 18%), urinary tract infection (UTI) (23% versus 13%), pain in extremity (17% versus 10%), upper abdominal pain (12% versus 3%), myalgia (7.7% versus 3.2%), and vaginal infections (6.2% versus 1.6%).

Treatment related TEAEs was slightly higher in the placebo group (50.8%) than the pooled tafamidis group (42.8%) and no particular TEAE was substantially more common in tafamidis recipients, although there were some differences. In the ATTR-PN studies, treatment related TEAEs showed an excess of urinary tract infection in the tafamidis group.

Discontinuations due to adverse events (AEs) were more frequent in the placebo group (28.8%) than the tafamidis group (18.2% for 20 mg and 22.7% for 80 mg). The most frequently reported individual TEAEs leading to discontinuation in any treatment group were cardiac failure, congestive cardiac failure, cardiac amyloidosis and disease progression.

Serious adverse event (SAE) were broadly balanced across treatment groups. The exposure-adjusted incidence rate (events per 100 patient-years) for patients reporting at

least one SAE was higher in placebo at 68.84 than in tafamidis 20 mg (57.35) and 80 mg (61.14) groups. The biggest difference in SAEs between groups was noted for cardiac disorders, which were less common on tafamidis than placebo.

Deaths were considered in the efficacy section above. In the pivotal study, Study B3461028, deaths were substantially more common in the placebo group (40.7%) than in the pooled tafamidis group (27.3%) and the incidence rate for deaths was significantly lower in the pooled tafamidis group than in the placebo group (the incidence rate ratio (95% CI) for tafamidis 20 mg, 80 mg, and pooled groups were: 0.60 (0.32, 1.13), 0.61 (0.37, 1.01), and 0.61 (0.39, 0.95), respectively). Most deaths were cardiac in nature, and for the non-cardiac deaths, no concerning patterns emerged. During the long term, follow-up study, interim analysis suggests that mortality has remained lower in subjects who received active treatment during the pivotal study, in comparison to those who received placebo in the pivotal study.

A similar percentage of patients in the tafamidis groups experienced laboratory abnormalities on-treatment (77.0% and 80.0%, respectively, in the 20 mg and 80 mg groups) compared with placebo (76.7%). For most analyses, the proportion of patients with new abnormally high or abnormally low values was similar in the placebo and tafamidis groups. The proportion of patients with abnormalities of troponin I showed marked variation across groups but levels were assessed in very few patients.

There did not appear to be evidence of liver toxicity. There was a small decrease in total thyroxine levels in both tafamidis dose groups, with a greater decrease observed for tafamidis 80 mg, however there were no significant changes from Baseline in free thyroxine or thyroid stimulating hormone. There were no intracranial neoplasms in the pivotal study but a Phase II (Study B3461025) study;[21] reported a case of glioblastoma multiforme. Post-market experience with the 20 mg strength raised no new safety issues, a 90 day safety update report raised no new issues, periodic benefit-risk evaluation reports did not identify new safety concerns and a 120 day safety update report with limited exposure to the 61 mg tafamidis free acid dose raised no new safety concerns, but the exposure was limited (n = 87) and uncontrolled.

## Risk management plan

The sponsor has submitted European Union-risk management plan (EU-RMP) version 9.0 (December 2018; data lock point (DLP) 1 August 2018) and Australian specific Annex (ASA) version 1.0 (24 January 2019) in support of these applications. At Round 2 the sponsor provided updated EU-RMP version 9.1 (31 July 2019; DLP 1 August 2018) and ASA version 1.1 (17 October 2019).

The sponsor has proposed summary of safety concerns and their associated risk monitoring and mitigation strategies as shown in the table below.[22]

[21] The Effects Of Fx-1006A On transthyretin stabilization and clinical outcome measures in patients with V122I or wild-type TTR amyloid cardiomyopathy. ClinicalTrials.gov Identifier: NCT00694161. Also known as Study FX1B-201

[22] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
*Routine pharmacovigilance* practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

**Table 4: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | Nil | – | – | – | – |
| **Important potential risks** | Hepatotoxicity | ✓‡ | ✓* | – | – |
| | Reproductive and developmental toxicity and lactation | ✓ | ✓*† | ✓ | – |
| | Changes in thyroid function, particularly in pregnant women | ✓‡ | ✓* | –§ | – |
| **Missing information** | Patients with NYHA class IV (ATTR-CM indication) | ✓ | ✓* | –§ | – |
| | Patients with severe hepatic impairment | ✓ | ✓* | ✓ | – |
| | Safety and efficacy in patients with ATTR-PN mutations other than Val30Met€ | ✓ | ✓* | – | – |

* Clinical studies
‡ Data capture aids to follow up adverse drug reaction reports
† Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) program including Australian patients
§ The sponsor has included wording relating to these risks in the PI and this is considered routine risk minimisation. The sponsor has been requested to update the ASA accordingly.
€ Val30Met represents substitution of valine with methionine at position 30.

The RMP evaluator considers the summary of safety concerns to be acceptable.

The sponsor has proposed routine pharmacovigilance and the use of data capture aids to collect additional information on hepatotoxicity and thyroid disorders. The sponsor has proposed additional clinical studies for all safety concerns and an enhanced surveillance program to monitor reproductive and developmental toxicity and lactation. The sponsor has confirmed Australian patient involvement in the Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) program. The RMP evaluator considers the pharmacovigilance plan to be acceptable.

The sponsor has proposed routine risk minimisation activities for patients with severe renal impairment, and use in pregnancy and lactation.

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The sponsor has differentiated tafamidis and tafamidis meglumine using the trade names Vyndamax and Vyndaqel, respectively. As requested, the sponsor has added wording to the Consumer Medicines Information (CMI) to indicate that Vyndamax and Vyndaqel are not bioequivalent.

The sponsor has proposed no additional risk minimisation activities. The RMP evaluator considers the risk minimisation plan to be acceptable.

There are no outstanding recommendations from an RMP perspective. Both substances will be included in the Black Triangle Scheme.

## Risk-benefit analysis

### Delegate's considerations

Tafamidis and tafamidis meglumine are two new chemical entities for the treatment of ATTR-CM that are supported by a well-designed, single pivotal study that demonstrated a statistically and clinically significant reduction in combined all-cause mortality and cardiovascular related hospitalisation. Significant benefit was also observed for each component of the combined endpoint. The primary endpoint became evident at 18 months of treatment and was supported by significant results for key secondary endpoints that first appeared at 6 months (6MWT and KCCQ-OS). The pivotal study was noted to have followed the EU guideline on the treatment of cardiac failure;[9] with an appropriate study design that was supported by the FDA and EMA. The efficacy variables and outcomes were appropriate, apart from terminological uncertainties surrounding the 'TTR stabilisation' definition. The ATTR-CM indication has been approved by the FDA and although an earlier submission to register tafamidis for ATTR-PN was not approved by the FDA, there did not appear to be substantial safety concerns.

Subgroup analysis of the pivotal study suggested a poorer overall prognosis in subjects with variant TTR compared to wild type genotype. The primary endpoint did not demonstrate a statistically significant treatment effect in variant TTR but this may be due to reduced power (mortality was lower in tafamidis recipients relative to placebo but the frequency of hospitalisation was higher). TTR stabilisation was also less with variant type compared to wild type. Two variant genotypes in 3 subjects in the pivotal study on 80 mg tafamidis meglumine did not demonstrate TTR stabilisation. In the sponsor's response to the clinical evaluation report on this issue, they discuss the lack of stabilisation was due to TTR values that were below the limit of quantitation at the Baseline visit, TTR concentrations remain elevated during the study and that the sponsor believes there is efficacy in these genotypes. However, given the small numbers it is difficult to draw clear conclusions.

Subgroup analysis of the pivotal study by NYHA class showed the effect of tafamidis in NYHA class III favoured but was not statistically significant for all-cause mortality and showed significantly higher CV related hospitalisation compared to placebo. The sponsor suggested that this increase in hospitalisation frequency could be the result of sicker patients surviving longer on tafamidis which may be reasonable. There is a lack of data in NYHA class IV but this may be best left as a clinical decision.

The interim analysis of the long-term extension of the pivotal study suggested that benefit was maintained during long-term treatment.

The safety profile of tafamidis meglumine was acceptable at doses of 20 mg or 80 mg daily and the pivotal study demonstrated no consistent safety signals apart from a slight reduction in total thyroxine levels on both doses which was greater on 80 mg than 20 mg. However, no statistically or clinically significant changes from Baseline in free thyroxine or thyroid stimulating hormone were observed and the sponsor has included a statement in the PI, although monitoring is not proposed. The exposure set was overall limited to detect uncommon or rarer AEs. However, the percentages of patients in the tafamidis treatment group who experienced TEAEs, severe AEs and SAEs were generally similar in tafamidis recipients and placebo recipients. The most commonly reported SAEs included cardiac failure and related terms, which were likely related to the underlying disease in this study population. Mortality was favourably affected by tafamidis, with significant benefits over placebo in the pivotal ATTR-CM study. Discontinuations due to AEs were less common in the tafamidis groups than in the placebo group. Safety during the long-term extension of the pivotal study appeared to be satisfactory. Potential adverse drug reactions identified in the pivotal ATTR-PN study (diarrhoea, urinary tract infection, vaginal infection and abdominal pain) did not appear to be associated with tafamidis use in the pivotal ATTR-CM study. Postmarketing surveillance of tafamidis exposure has raised no new safety issues. An acceptable RMP has been provided.

Preclinical studies suggested that tafamidis may cause liver abnormalities at exposures comparable to those likely to be produced in humans but there did not appear to be a clinical signal. The Periodic Benefit-Risk Evaluation Reports (PBRER) noted isolated hepatic AEs were observed, but there was no evidence of a causal relation with tafamidis. In the polyneuropathy program, a single Hy's law;[23] case was thought to be unlikely related to tafamidis. The low numbers of patients exposed to tafamidis therefore does not preclude a risk of hepatotoxicity.

Intracranial neoplasms were a concern from the ATTR-PN studies due to four reports of primary intracranial neoplasm. However, the pivotal ATTR-CM study did not identify any cases but there was one glioblastoma multiforme reported in a Phase II study on a 20 mg dose. The evaluator considered it unlikely that tafamidis is associated with an increased risk given the lack of a signal in the larger pivotal ATTR-CM study, which also used a higher dose, but this should remain of interest in post-market surveillance, given the limited dataset.

The sponsor is proposing dosing with the higher dose only of 80 mg tafamidis meglumine daily (or 61 mg tafamidis free acid daily). Most efficacy variables showed a numerically similar benefit between the 20 mg and 80 mg dose groups, but NT-proBNP results suggested a better profile with 80 mg. In the long term extension of the pivotal study, a small mortality benefit is suggested in the higher dose group, relative to the lower dose group, based on a post-hoc analysis but this did not achieve statistical significance. The safety profile of tafamidis meglumine 80 mg appeared to be broadly similar to that of tafamidis meglumine 20 mg. Given the above, the data supporting the proposed dose of 80 mg is, on balance, acceptable, although the evidence is not strong. The clinical evaluator commented that the optimal dose may not have been identified, however given the efficacy results in the pivotal study, this would not preclude registration of the proposed dose.

[23] **Hy's Law**: Evidence of hepatocellular injury with alanine aminotransferase and/or aspartate aminotransferase > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin.

The population PK analysis showed tafamidis meglumine levels to be substantially reduced in subjects with hepatic impairment, therefore querying whether a dose adjustment is needed. However, the sponsor has indicated that the reduced exposure is unlikely to be clinically significant because subjects with hepatic impairment also have lowered TTR levels. The evaluator commented that it therefore appears likely that many subjects with hepatic impairment will experience similar TTRR during tafamidis treatment to those seen in subjects without hepatic impairment, however this remains an issue.

The pivotal study used 4 x 20 mg tafamidis meglumine capsules to support the 80 mg daily dose proposed for registration but not the proposed 61 mg daily dose of tafamidis (free acid), however acceptable bioequivalence data have been provided to support both products at their respective doses. The exposure to the 61 mg tafamidis formulation was limited but tolerability is expected to be similar to the 80 mg dose of tafamidis meglumine. The 120 day safety update report included limited exposure to the 61 mg formulation from the extension study of the pivotal study but did not appear to raise new safety concerns. There were different food effects for the two formulations which could lead to tolerability issues related to $C_{max}$. However, given the safety profile then this is unlikely to be a significant issue. Both products are proposed to be taken with or without food.

### Data deficiencies and outstanding Issues

Outstanding issues from a quality perspective were subsequently resolved post second round evaluation.

The submission relies on a single pivotal Phase III study with limited exposure at the proposed dose for ATTR-CM (n = 176) therefore uncommon or rarer AEs may not have been detected.

Amyloid deposition in the myocardium was not directly measured in the pivotal study.

There were concerns with the definition of TTR stabilisation and its clinical implications.

The study was not designed or powered to compare both doses of tafamidis meglumine and no adequate dose ranging study was submitted.

Exposure data for the 61 mg tafamidis dose is very limited and its safety and efficacy rely on bioequivalence with the 80 mg tafamidis meglumine dose.

Tafamidis has not been studied in NYHA class IV patients or those with severe hepatic impairment. Limited data are available in subjects with renal impairment.

Tafamidis has not been assessed in the setting of pregnancy (tafamidis is Category D in pregnancy);[6] or lactation.

### Proposed regulatory action

Pending advice from the Advisory Committee on Medicines (ACM) and the sponsor's pre-ACM response, the Delegate considers the benefit/risk profile to be positive and recommends approval for the indication:

> *Vyndaqel is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*
>
> *Vyndamax is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*

## Proposed conditions of registration

### *Vyndaqel (tafamidis meglumine)*

- The Vyndaqel EU- RMP (version 9.1, dated 31 July 2019, DLP 1 August 2018), with ASA (version 1.1, dated 17 October 2019), included with submission PM-2019-01399-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Vyndaqel (tafamidis meglumine) is to be included in the Black Triangle Scheme. The PI and CMI for Vyndaqel must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

### *Vyndamax (tafamidis)*

- The Vyndamax EU-RMP (version 9.1, dated 31 July 2019, DLP 1 August 2018), with ASA (version 1.1, dated 17 October 2019), included with submission PM-2019-00391-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the EMA's Guideline on GVP Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Vyndamax (tafamidis) is to be included in the Black Triangle Scheme. The PI and CMI for Vyndamax must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## Questions for the sponsor

1. Please provide an update on the number of cases of intracranial neoplasms reported from all studies and post-marketing reports with tafamidis.

2. Please comment on the clinical evaluator's recommendation that post-marketing studies should be performed to assess TTRR in a much larger sample of subjects with hepatic impairment.
3. Please comment on the clinical evaluator's comment that further studies should be considered to clarify the optimal dose.
4. The FDA commented that fall related SAEs was doubled in the tafamidis groups compared to placebo. Please comment on this finding and the sponsor's proposal to address this concern.

**Sponsor's response**

*1. Please provide an update on the number of cases of intracranial neoplasms reported from all studies and post-marketing reports with tafamidis.*

The tafamidis interval summary tabulation of SAEs from all clinical trials from 16 May 2018 to 15 May 2019 (tenth PSUR) reported 1,802 cases and 2,686 SAEs. No new SAE of intracranial neoplasm was reported in that period.

In the tafamidis PSUR prepared for Japan and covering the period from 16 May 2019 through 15 November 2019, no new intracranial neoplasms were reported for clinical trials or for post-marketing sources during the interval period.

*2. Please comment on the clinical evaluator's recommendation that post-marketing studies should be performed to assess TTRR in a much larger sample of subjects with hepatic impairment.*

As described in the response to a PK question, dated 31 October 2019, the tafamidis:TTR stoichiometry, requiring an evaluation of not only plasma tafamidis concentrations but serum protein levels, specifically transthyretin, is of relevance to stabilisation of the TTR tetramer in subjects with hepatic impairment. Such a study has been conducted consistent with EMA and FDA guidance, wherein the results based on a similar TTRR stoichiometry compared to those without hepatic impairment, suggest that patients with moderate hepatic impairment would be expected to demonstrate effective stabilisation of the TTR tetramer following chronic dosing with tafamidis once daily.

Indeed, TTR concentrations in moderate hepatic impairment subjects (see Table 5) were consistent with reported levels in other patients with liver disease.[24] In the ATTR-ACT trial (Study B3461028), subjects with hepatic impairment were permitted and no specific concerns were identified in those patients. Consequently, the sponsor does not believe a post-marketing assessment of TTRR in a much larger sample of subjects with hepatic impairment is warranted as an additional study in a larger group is not expected to yield further information to assure the safe and effective use of tafamidis. Finally, it would be highly challenging to recruit a large sample size with hepatic impairment in an already orphan disease (ATTR-CM) population.

[24] Yasmin MY et al. (1993). Prealbumin rather than albumin in a more sensitive indicator of acute liver disease. *Malays J Pathol*, 15(2):147-50.

**Table 5: Study B3461016 Summary of transthyretin and albumin by hepatic function (Stage 1, all subjects)**

| | TTR (pre-albumin) (mg/dL) N=9 | | Albumin (g/L) N=9 | |
|---|---|---|---|---|
| Visit | Healthy | Moderate | Healthy | Moderate |
| Screening | | | | |
| Mean (SD) | 28.0 (5.13) | 12.4 (6.81) | 40.2 (1.99) | 22.2 (12.78) |
| Range | 21.5, 36.5 | 3.4, 25.7 | 37.0, 43.0 | 2.2, 40.0 |
| CV (%) | 18.31 | 55.00 | 4.94 | 57.54 |
| Day 1 | | | | |
| Mean (SD) | 24.3 (4.51) | 10.7 (5.92) | 36.2 (2.64) | 25.7 (7.33) |
| Range | 18.2, 33.3 | 3.6, 20.3 | 31.0, 39.0 | 16.0, 37.0 |
| CV (%) | 18.55 | 55.41 | 7.28 | 28.56 |
| Day 2 | | | | |
| Mean (SD) | 26.1 (5.82) | 11.1 (5.59) | 36.7 (1.87) | 21.9 (9.39) |
| Range | 19.0, 38.8 | 4.6, 20.5 | 34.0, 40.0 | 3.3, 37.0 |
| CV (%) | 22.29 | 50.44 | 5.10 | 42.84 |
| Day 16 | | | | |
| Mean (SD) | 25.0 (4.65) | 11.8 (6.83) | 37.0 (4.39) | 27.3 (6.89) |
| Range | 16.2, 29.8 | 3.6, 21.3 | 28.0, 42.0 | 17.0, 39.0 |
| CV (%) | 18.63 | 57.94 | 11.86 | 25.21 |

TTR = transthyretin; N = number of subjects; SD = standard deviation; CV = coefficient of variation.
Note: Moderate hepatic dysfunction is defined as a Child-Pugh score of 7 to 9, inclusive.
Study B3461016: Pharmacokinetics of orally administered FX-1006A in subjects with hepatic dysfunction; also referred to as Study Fx1A-105; ClinicalTrials.gov Identifier: NCT01358565.

3. *Please comment on the clinical evaluator's comment that further studies should be considered to clarify the optimal dose.*

In the response to ACM Question 3 dated 31 October 2019, the sponsor described the dose selection process for the pivotal ATTR-CM study and the choice for treatment of these patients. Use of 80 mg achieves a higher degree of TTR stabilisation, which is an important consideration as it maintains more TTR in the functional tetrameric form and lowers the amount of monomeric TTR available for amyloidogenesis. It has been demonstrated that the 80 mg dose produces TTRR molar ratios approaching or on the target plateau region of TTR % stabilisation and the 20 mg dose results in TTR stabilization well below the plateau. The sponsor acknowledges that these differential pharmacodynamic effects favouring 80 mg are not as clearly reflected in the clinical outcomes at Month 30 but a dose response on survival emerges in favour of 80 mg with longer term treatment (blinded to dose) and are supported by corresponding reductions in NT-proBNP levels. Consequently, chronic treatment with the 80 mg tafamidis dose is well justified in ATTR-CM, a life-threatening and progressively fatal disease.

The sponsor understands the evaluator's comment to encourage exploration of doses between 80 mg and 20 mg once daily. The sponsor expects the effect size would be even smaller than that observed between 80 mg and 20 mg in the pivotal trial, requiring a larger or longer study to have sufficient power to differentiate between doses and in light of no dose-limiting AEs, likely not to be able to demonstrate a more optimal benefit/risk profile. In an orphan disease setting, conduct of large studies is inherently difficult due to the rarity of the condition. It should be noted that such consideration also previously informed the design of the pivotal trial, which was *a priori* not powered for individual dose comparisons to placebo but instead compared pooled tafamidis to placebo. Lastly, given the near maximal degree of TTR stabilisation at 80 mg, large increases in doses beyond 80

mg would likely result in marginal increases in TTR tetramer stabilisation and unknown or undifferentiated clinical benefit. As such, the sponsor considers further dose exploration studies to be uninformative and/or infeasible.

In view of the available evidence, the sponsor concludes that the 80 mg dose achieves the target pharmacodynamic biomarker response, clinical efficacy, and maintains a favourable safety profile thus providing an overall positive benefit/risk profile for the treatment of ATTR-CM.

4. *The FDA commented that fall related SAEs was doubled in the tafamidis groups compared to placebo. Please comment on this finding and the sponsor's proposal to address this concern*.

In Study B3461028, SAEs of fall were reported at 5.7%, 5.1% and 2.8% in the 20 mg tafamidis group, the 80 mg and the placebo group, respectively. However, there were no differences between treatment groups in related events that might contribute to falls such as dizziness and hypotension.

A more comprehensive review of all TEAEs (serious and non-serious) of fall was performed for context and the following observations can be made:

In the pivotal Phase III Study B3461028, the ATTR-ACT trial, there was a numerically higher incidence of falls in patients treated with tafamidis 20 mg (n = 27 (30.7%)), compared with placebo (n=41 (23.2%)). However, this apparent increase was not dose-related, with a similar number of falls observed in the tafamidis 80 mg group (n = 43 (24.4%)), compared to placebo, as observed for SAEs (5.7% at 20 mg and 5.1% at 80 mg tafamidis, respectively). The incidence of treatment-related falls was also similar across treatment arms (n = 1 (1.1%), n = 0 and n = 1 (0.6%) in the tafamidis 20 mg, tafamidis 80 mg and placebo groups, respectively).

In addition to the lack of dose-related increase in falls, no correlation was observed between the incidence of falls and that of other AEs which may be related to falls (see Table 6). Both Preferred Terms (PTs) of dizziness and fatigue were reported at similar incidences in the placebo and tafamidis 20 mg arms, and at slightly lower incidences among patients treated with tafamidis 80 mg. Although balance disorder was increased among patients treated with tafamidis 80 mg, this did not correlate with the increased incidence of falls, which was observed only in the tafamidis 20 mg group.

**Table 6: Study B3461028 Incidence of adverse events potentially related to falls in ATTR-ACT trial, all causalities**

| Preferred term | Tafamidis 20 mg N=88 n (%) | Tafamidis 80 mg N=176 n (%) | Placebo N=177 n (%) |
|---|---|---|---|
| Dizziness | 17 (19.3) | 25 (14.2) | 37 (20.9) |
| Fatigue | 16 (18.2) | 29 (16.5) | 33 (18.6) |
| Balance disorder | 2 (2.3) | 15 (8.5) | 2 (1.1) |

Source: (S0000 Module 5.3.5.1 B3461028 Clinical Study Report)
Abbreviations: AE = adverse event; mg = milligram; n/N = number

A possible contributing factor to the higher incidence of falls observed in the tafamidis 20 mg group was the numerically increased use of walking aids at Baseline in this group. Among patients allocated to treatment with tafamidis 20 mg, 11.4% (n = 10) reported the use of a walking aid, compared with 6.8% (n = 12) and 6.2% (n = 11) in the tafamidis 80 mg and placebo groups, respectively.

Orthostatic hypotension was specifically evaluated during Phase II and III studies, with the following PTs utilised to identify AEs potentially related to orthostatic hypotension:

diastolic hypotension, hypotension, orthostatic hypotension, procedural dizziness, dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness and fall. In Study B3461028, the ATTR-ACT trial, the exposure-adjusted incidence rate (EAIR) per 100 patient-years of patients reporting at least one AE associated with orthostatic hypotension was similar across the tafamidis and placebo-treated treatment groups. Across all tafamidis-treated patients in the ATTR-CM clinical program, no signal was observed for orthostatic hypotension, dizziness or fall.

Additionally, events of fall were reported in patients treated with tafamidis in the clinical trials, where most of the patients were elderly and at increased risk of fall. In Study B3461028, the proportion of fall for patients treated with tafamidis was 30.7% and 23.2% in the tafamidis 20 and 80 mg groups, respectively (Table 7), which appears to be within the reported range of frequency of fall in the elderly population. A publication reported the annual incidences of fall as 30% to 40% for individuals > 65 years old and 50% for individuals ≥ 80 years.[25]

The EAIRs for placebo-controlled Study B3461028 are provided in Table 7. The EAIR point estimate for the 20 mg group was slightly higher than the IRs for the placebo and the 80 mg groups; however, the following can be noted:

- Sample size: A higher incidence rate in the 20 mg group may be attributed to potential increased variability in a smaller sample size in the 20 mg group versus 80 mg and placebo (n = 88, 176, and 177, respectively).
- Lack of statistical significance: When comparing to the placebo group, the 95% CI of the incidence rate difference (IRD) for both 20 and 80 mg groups included zero, suggesting no statistical difference in incidence rates of fall between each of the 2 dose groups and placebo.
- Lack of dose response: With a 4 fold increase in dose (20 to 80 mg tafamidis) no increase in IR of fall was observed. The IR rates for placebo and 80 mg were comparable.

**Table 7: Study B3461028 Proportions and exposure-adjusted incidence rates for treatment-emergent adverse event of fall (cohort) (all causalities)**

| SOC PT | Treatment Group | N | SY | n (%) | IR (95% CI) | IRD (95% CI) | IRR (95% CI) |
|---|---|---|---|---|---|---|---|
| Fall | Placebo | 177 | 297.66 | 41 (23.2) | 13.77 ( 9.88, 18.69) | | |
| | Tafamidis 20 mg | 88 | 158.07 | 27 (30.7) | 17.08 (11.26, 24.85) | 3.31 (-4.39,11.01) | 1.24 (0.76, 2.02) |
| | Tafamidis 80 mg | 176 | 316.04 | 43 (24.4) | 13.61 (9.85,18.33) | -0.17 (-6.03,5.69) | 0.99 (0.64, 1.52) |

SOC = system organ class; PT = Preferred Term; N = number of treated subjects; SY = subject years of exposure; follow-up period = up to the last dose + 28 days; n = number of subjects with event reported during the follow-up period; CI = confidence interval;
For a particular event, SY is the sum across subjects of years up to the first event or the end of follow-up period for subjects who did not have the event.
IR = Incidence rate defined as the number of subjects with an event per 100 SY with 95% CI calculated using an exact method assuming the number of events in a fixed interval of time follows a Poisson distribution.
IRD = Incidence rate difference (tafamidis - placebo) with 95% CI obtained using the Wald method.
IRR = Incidence rate ratio (tafamidis/placebo) with 95% CI estimated using Poisson regression with treatment group in the model.

[25] Kiel DP. UpToDate: Falls in older persons. Apr 25, 2018. https://www.uptodate.com/contents/falls-inolder-persons-risk-factors-and-patient-evaluation. Accessed 17 January 2019.

Additionally, in the ATTR-PN population double blind placebo controlled Study B3461020;[26] there were zero falls in 20 mg group (n = 65) and 1 fall in the placebo group (n = 63, 1.6%).

In conclusion, data from our controlled studies in both ATTR-CM and ATTR-PN do not suggest an associated increased incidence of fall events with tafamidis administration and therefore no additional measures are warranted.

### Request for Advisory Committee on Medicines advice

The committee is requested to provide advice on the following issues:

1. What are the Committee's views on the appropriate dose of tafamidis meglumine for ATTR-CM?
2. What are the Committee's views on the efficacy of tafamidis meglumine in patients with NYHA class III ATTR-CM?
3. What are the Committee's comments on the efficacy of tafamidis meglumine in patients with variant TTR?
4. What are the Committee's comments on the safety profile of tafamidis, given the limited exposure dataset?
5. Have the questions and advice previously provided by ACM been adequately addressed?

### Advisory Committee considerations[7]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM considered these products to have an overall positive benefit-risk profile for the indications:

> *Vyndaqel is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*
>
> *Vyndamax is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*

#### *Specific advice*

The ACM advised the following in response to the Delegate's specific request for advice:

***1. What are the Committee's views on the appropriate dose of tafamidis meglumine for ATTR-CM?***

The ACM noted that uncertainty exists regarding the optimal dosing for tafamidis. While there is no significant difference in efficacy between the two doses, the 80 mg dose outcomes appear to be slightly more favourable compared to the 20 mg dose, so the ACM indicated a preference for the 80mg dose. There were no major safety concerns with either formulation or dose.

[26] Study B3461020: Safety and efficacy study of Fx-1006A in patients with familial amyloidosis; also known as Study FX-005; ClinicalTrials.gov Identifier: NCT00409175.

**2. *What are the Committee's views on the efficacy of tafamidis meglumine in patients with NYHA class III ATTR-CM?***

The ACM advised that ideally, tafamidis would be administered to patients prior to reaching NYHA class III ATTR-CM, as the major efficacy benefits were demonstrated in patients with classes I and II. The ACM did consider whether the disease in patients with NYHA class III ATTR-CM is too far advanced to derive benefit from tafamidis, ultimately considering the efficacy in Class III to be acceptable, noting that the PI includes information about the efficacy outcomes in Class III.

***3. What are the Committee's comments on the efficacy of tafamidis meglumine in patients with variant TTR?***

The ACM concluded that while there is a spectrum of disease due to variants, the data presented provides no reason to assume that the response to treatment will vary in the different variants. The ACM was supportive of the use of tafamidis meglumine in patients with variant TTR.

***4. What are the Committee's comments on the safety profile of tafamidis, given the limited exposure dataset?***

The ACM does not have any significant safety concerns with the use of tafamidis based on the data provided to date. The committee considered that tafamidis is intended for use in a relatively small population who have limited alternatives for treatment.

***5. Have the questions and advice previously provided by ACM been adequately addressed?***

The ACM advised that the previous questions asked by the committee and the answers provided by the sponsor were adequate and resulted in the provision of additional safety data.

## Outcome

### Vyndamax

Based on a review of quality, safety and efficacy, the TGA approved the registration of Vyndamax (tafamidis) 61 mg soft gelatin capsules, indicated for:

> *Vyndamax is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*

### Vyndaqel

Based on a review of quality, safety and efficacy, the TGA approved the registration of Vyndaqel (tafamidis meglumine) 20 mg soft gelatin capsules, indicated for:

> *Vyndaqel is indicated for the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).*

### Specific conditions of registration applying to these goods

***Vyndamax***

- Vyndamax (tafamidis) is to be included in the Black Triangle Scheme. The PI and CMI for Vyndamax must include the black triangle symbol and mandatory accompanying

text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The Vyndamax EU-RMP (version 9.1, dated 31 July 2019, data lock point 1 August 2018), with ASA (version 1.1, dated 17 October 2019), included with submission PM-2019-01399-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on GVP Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

***Vyndaqel***

- Vyndaqel (tafamidis meglumine) is to be included in the Black Triangle Scheme. The PI and CMI for Vyndaqel must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Vyndaqel EU-RMP (version 9.1, dated 31 July 2019, data lock point 1 August 2018), with ASA (version 1.1, dated 17 October 2019), included with submission PM-2019-01399-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on GVP Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

# Attachment 1 and 2. Product Information

The PIs for Vyndamax and Vyndaqel approved with the submission which is described in this AusPAR is at Attachment 1 and Attachment 2. For the most recent PIs, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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Reference/Publication #