12 December 2019
EMA/3391/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyndaqel

International non-proprietary name: tafamidis

Procedure No. EMEA/H/C/002294/X/0049/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

6MWT	6-Minute Walk Test
ACE	Angiotensin-converting enzyme
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTRm	variant transthyretin amyloid
ATTR-PN	transthyretin amyloid polyneuropathy
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time zero to infinity
BA	bioavailability
BE	bioequivalence
CHF	congestive heart failure
CL/F	apparent clearance
CM	cardiomyopathy
$C_{max\ ss}$	maximum plasma concentration at steady state
C_{min}	minimum observed concentration
%CV	%Coefficient of Variation
EAC	Endpoint Adjudication Committee
EAP	Early Access Program
EC_{50}	concentration corresponding to 50% of the maximum effect
ECG	electrocardiogram
ECHO	echocardiography
E-DMC	External Data Monitoring Committee
Emax	maximal response
FAP	familial amyloid polyneuropathy
GD	gestation day
GI	gastrointestinal
hATTR	hereditary transthyretin amyloidosis
HR	hazard ratio
HV	healthy volunteer
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I. P
IRR	incidence rate ratio
ITT	intent to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
Kd	dissociation constant
Leu111Met	leucine replaced by methionine at position 111
LFT	liver function test
LLN	lower limit of normal
LTE	long term extension
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
PMS	post market surveillance
Pro24Ser	proline replaced by serine at position 24 of the TTR protein
PSUR	Pharmacovigilance Safety Update Report
PT	preferred term
QD	once a day
QOL	quality of life
QTc	corrected QT interval
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party

SD	single dose
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey
SSA	senile systemic amyloidosis
T_4	total thyroxine
TBG	thyroxine binding globulin
TEAE	treatment-emergent adverse event
TESPO	Tafamidis Enhanced Surveillance Pregnancy Outcomes
THAOS	Transthyretin-Associated Amyloidoses Outcomes Survey
T_{max}	time to reach C_{max}
TRACS	Transthyretin Amyloidosis Cardiac Study
TSH	thyroid-stimulating hormone
TTR	transthyretin
TTR-FAP	transthyretin familial amyloid polyneuropathy
TTRR	tafamidis:TTR
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
Val20Ile	valine replaced by isoleucine in position 20 of the TTR protein
Val122Ile	valine replaced by isoleucine at position 122
Val30Met	valine replaced by methionine at position 30

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Europe MA EEIG submitted on 7 January 2019 a group of variations consisting of extension of the marketing authorisation and the following variation:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Extension application to:
- introduce a new strength (61 mg soft capsules, pack-size of 30 and 90 capsules) and a new indication for the "treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM)"
- introduce qualitative change in declared active substance (tafamidis) not defined as a new active substance;
This is grouped with a type II variation (C.I.4) to update sections 4.6 of the Vyndaqel (tafamidis meglumine) 20 mg soft capsules SmPC to add wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme.

In addition, the submission of an updated RMP version 9.0 in order to include the proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical program and post marketing reporting, reclassification of the safety concerns, removal of HCP educational leaflet. Relevant changes are also proposed for Annex II of the product information.
The MAH is also proposing an update to Section 16 Information in Braille of Annex IIIa - Labelling (carton) to differentiate between the dosage forms.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Vyndaqel was designated as an orphan medicinal product in the 2 following conditions, covering the claimed targeted ATTR-CM indication:

- Familial Amyloid Polyneuropathy (TTR-FAP, now ATTR-PN) (EU/3/06/401) on 28 August 2006. At the time of designation, hereditary ATTR affected below 0.1 in 10,000 people. In 2012, the COMP confirmed that the existing orphan designation for 'treatment of TTR-FAP' includes all phenotypes of hereditary ATTR, including variant ATTR-CM, even in the absence of polyneuropathy symptoms.
- Senile systemic amyloidosis (SSA; EU/3/12/1066) on 8 November 2012. At the time of designation, ATTR wild type (previously known as SSA) affected approximately 3 in 10,000 people in the EU.

In accordance with Art 5(12) of Regulation (EC) No 141/2000 the Committee for Orphan Medicinal Products shall review the criteria provided therein and issue an opinion on the maintenance of the orphan designation, which will subsequently be provided to the European Commission to be taken into consideration in the decision making process.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (decision number: P/147/2010; waiver number: EMEA-000884-PIP01-10) issued on 11 June 2010 on the granting of a product-specific waiver in all subsets of the paediatic population for the condition *"neuropathic heredofamilial amyloidosis",* on the grounds that tafamidis does not represent a significant therapeutic benefit for paediatric patients as clinical studies are not feasible in this patient population.

In January 2018, the PDCO confirmed that '*treatment of cardiomyopathy due to wild-type or variant transthyretin in adults*' is considered covered by the condition in the previously mentioned decision.

Additionally, it was confirmed in February 2018 that this waiver covers applications where it will be established that tafamidis free acid is the same active substance as tafamidis meglumine (e.g, an extension to existing tafamidis meglumine marketing authorisation).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products Onpattro and Tegsedi.

Derogation(s) from market exclusivity

Not applicable.

Additional Data exclusivity/Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific Advice

The MAH received scientific advice from the CHMP on the development for the indication from the CHMP on 21 June 2012 (EMEA/H/SA/1074/2/2012/III), 30 May 2013 (EMEA/H/SA/1074/2/FU/1/2013/II), 28 April 2016 (EMEA/H/SA/1074/3/2016/II), 15 September 2016 (EMEA/H/SA/1074/3/FU/1/2016/II), 26 January 2017 (EMEA/H/SA/1074/3/FU/2/2016/II), 13 March 2017 (EMEA/H/SA/1074/3/FU/2/2016/II Clarification Letter) and 20 July 2017 (EMEA/H/SA/1074/3/FU/3/2017/II). The scientific advice pertained to non-clinical, and clinical aspects (please, see section *Type of Application and aspects on development* in chapter 2.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: Bruno Sepodes

The application was received by the EMA on	7 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	30 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 April 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	29 May 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	14 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	17 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2019
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	17 October 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 November 2019
The Rapporteurs circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 November 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vyndaqel on	12 December 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication claimed by the Applicant for VYNDAQEL 61mg (micronized tafamidis) is the treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation.

This disease, also called ATTR-CM in this document, is caused by the accumulation of misfolded transthyretin (TTR) amyloid fibrils in the myocardium. It leads to restrictive cardiomyopathy and heart failure, and ultimately death.

ATTR CM can be of 2 types:

- hereditary ATTR-CM, also called familial, mutant or variant ATTR-CM, when inherited by mutation in the TTR gene,

- wild-type ATTR-CM, also called senile or non-variant ATTR-CM, when TTR becomes structurally unstable with age.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Hereditary ATTR-CM is a rare disease. When including all phenotypes of hereditary ATTR (characterized by cardiac and/or and polyneuropathy symptoms), the prevalence was estimated to be below 0.1 in 10,000 people in the EU.

The Val122Ile mutation allele associated with variant ATTR-CM occurs in 3.3% to 4.0% of the US African-American population and is exceedingly rare in White patients (Buxbaum et al. 2006, Quarta et al. 2015).

The prevalence of wild-type ATTR-CM is also defined as rare. This cardiac disease is part of a senile systemic amyloidosis (or wild-type ATTR) characterized by combination of various symptoms, depending on the organ involve (mostly in the kidneys, heart, gastrointestinal tract, skin and tenosynovial tissue). Common clinical features are cardiac dysfunction, renal dysfunction, carpal tunnel syndrome and spinal canal stenosis. The prevalence of wild-type ATTR was estimated to be approximately 3 in 10,000 people in the EU.

Though prevalence of wild-type ATTR-CM is uncertain, studies report a prevalence of 13% in heart failure patients with preserved ejection fraction (Gilmore et al. 2016, Gonzalez-Lopez 2015), 16% in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis (Castano et al. 2016), and 5% of patients with presumed hypertrophic cardiomyopathy (Damy et al. 2016).

ATTR-CM typically occurs in patients aged 60 years or older, though the Leu111Met variant may express ATTR-CM in patients at an earlier age (Rapezzi et al. 2010).

ATTR-CM is currently associated with mean progression to death within 2 to 3 years (median survival 25.6 months) of diagnosis for variants and up to 5 years (median survival 43.0 months) for wild type, with most patients dying from cardiac causes (Ruberg et al. 2012 and Grogan et al.2016).

2.1.3. Aetiology and pathogenesis

TTR amyloidosis is a disease caused by the destabilisation and dissociation of the native TTR tetramer which can result in misfolding and the formation of amyloid fibrils and progressive amyloid deposition in tissues.

The 2 major phenotypes which form the spectrum of ATTR amyloidosis are ATTR-CM which primarily affects the myocardium, and ATTR-PN, also referred to as transthyretin familial amyloid polyneuropathy (TTR-FAP), which primarily affects the peripheral and autonomic nerves. These clinical manifestations may occur in isolation or together. Both result in progressively impaired function, and ultimately in death.

ATTR-CM is a fatal disorder, characterised by the deposition of misfolded TTR amyloid fibrils in the ventricular walls (extra-myocardial), causing progressive disruption in the ability of the heart to effectively pump blood through the circulatory system. In ATTR-CM, the myocardium is the key site of ATTR deposition, and accumulation can lead to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure.

ATTR-CM can be inherited as an autosomal dominant trait caused by mutation in the TTR gene (also known as familial amyloid cardiomyopathy), or by deposition of wild-type TTR protein, previously called senile systemic or senile cardiac amyloidosis (Jacobson et al. 1997, Saraiva 1995).

There are more than 120 mutations in the TTR gene which cause a variable phenotype determined by the relative extent of amyloid deposition in the myocardium and peripheral nerves. ATTR-CM is associated with genetic variants of TTR such as Val122Ile and Leu111Met (Rosenblum et al. 2018, Jacobson et al. 1997).

In wild-type disease, TTR may become structurally unstable with age and result in deposition of amyloid fibrils, primarily in heart tissue (Saraiva 2001, Hammarström et al. 2002, Quintas et al. 2001).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The deposition and accumulation of misfolded TTR amyloid fibrils in the myocardium can lead to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure, with most patients dying from cardiac causes, including sudden death, congestive heart failure (CHF), and myocardial infarction.

ATTR-CM (due to both wild-type and variant TTR) uniformly presents with the typical symptoms of heart failure (restrictive cardiac disease), including shortness of breath, dyspnoea on exertion, orthostatic hypotension, syncope and dysrhythmias including atrial fibrillation.

Signs of ATTR-CM are assessed via tests performed as part of routine heart failure assessment, including electrocardiography, echocardiography, and cardiac biomarkers (eg, NT-proBNP). Findings from these objective measures of cardiac involvement include abnormal electrocardiogram (ECG) with findings including low voltage, left and right ventricular wall thickening by echocardiogram, and elevated cardiac biomarkers (Connors et al. 2009). These findings are non-specific for heart failure and/or co-morbid conditions are associated with congestive heart failure (i.e, diabetes, hypertension, etc), making the diagnosis of cardiac amyloidosis difficult, resulting in diagnosis delays and under diagnosis of ATTR-CM (Rapezzi et al. 2010, Ando et al. 2013, Connors et al. 2016).

The New York Heart Association (NYHA) Classification provides a simple way of classifying the extent of heart failure. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain. It is hypothesized that most diagnosed ATTR-CM patients have already

symptoms of heart failure, mild symptoms (NYHA Class II), marked limitation (NYHA Class III) or severe limitation even at rest (NYHA IV). Mostly hereditary ATTR-CM can be detected early, in a family context affecting multiple generations, even before cardiac symptoms (NYHA Class I).

More specific procedures are necessary for the identification of the disease:

- Genotyping: The genotyping test is a major tool that should be performed in patients of all age with suspicion of ATTR-CM, to identify whether it is hereditary ATTR-CM or not.

- Biopsy and bone scintigraphy: Definitive diagnosis of ATTR-CM had been dependent upon tissue biopsy, in combination with presence of symptomatic heart failure, when the pivotal study B3461028 was initially designed (Rapezzi et al. 2010). More recently, a non-biopsy approach using technetium-labeled bone scintigraphy tracers has emerged. This approach is considered highly sensitive and specific for diagnosing ATTR-CM in both hereditary and wild-type subjects (Gillmore et al. 2016, Castano et al. 2016, Bokhari et al. 2013). It could detect TTR amyloidosis prior to an increase in left ventricular wall thickness or the development of clinical syndrome of heart failure and a rise in cardiac biomarkers, making early identification and treatment more likely (Hag et al. 2017, Glaudemans et al. 2014, Galat et al. 2014).

- TTR identification: TTR precursor protein identification by immunohistochemistry or mass spectrometry and exclusion of light-chain amyloidosis (other types of amyloidosis, including AL amyloidosis, associated with multiple myeloma, which is an absolute emergency) has to be part of the diagnosis too, in order that patients receive the most immediate and adequate treatment for such severe disease.

Due to the different specific tests necessary to identify ATTR-CM without error of diagnosis, some specific algorithm for diagnosis of ATTR-CM should be used in order to allow better prognosis with early and adequate treatment of patients.

Wild-type ATTR-CM can be considered as a rare disease for the moment, but this may be partly due to underdiagnosis, in the absence of specific symptoms, and with the presence of high comorbidities, high age, and with the fact that the disease is unrecognised for the moment. However, there could be a risk of overdiagnosis or misuse, if the new tests for diagnosis are overspread, or criteria of diagnosis not well followed.

2.1.5. Management

There is currently no approved pharmacologic treatment specifically for ATTR-CM.

Treatments to manage ATTR-CM symptoms include a broad range of medications used to treat heart failure including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, and second generation calcium channel blockers. Except for these medications and pacemaker placement for cardiac arrhythmias, the only treatment option currently available for some ATTR-CM patients might be cardiac transplantation, or for some patients with variant type disease, orthotopic liver and/or heart transplant might be an option. Transplantation of the liver removes the primary production site of amyloidogenic variant TTR protein (Falk 2011, Lewis WD et al. 1994, Holmgren et al. 1993). Liver transplant may be combined with heart transplant, depending on organ availability, patient capacity to tolerate the combined transplant, and the severity of cardiac amyloidosis at the time of transplant. However, transplantation is often not an option for ATTR-CM patients given their advanced age at diagnosis, as well as their co-morbid burden of illness which increases the likelihood of morbidity and mortality associated with the procedure.

Given there are currently no approved pharmacological treatments for ATTR-CM, an ultimately fatal disease, and the risks and organ availability challenges associated with liver and heart transplantation, there is a significant unmet medical need for an effective and safe treatment to slow the progression of disease and improve patient outcomes.

Given the unmet medical need, Vyndaqel 20mg has been available at national level in some Member states to treat ATTR-CM (e.g more than 400 treated patients identified in France with VYNDAQEL 20mg once daily in April 2019).

Some other products are also studied in ATTR-CM with recruiting, ongoing or completed clinical trials, e.g antisense oligonucleotide (inotersen), small interfering RNA (revusiran, patisiran) or old products also known to disrupt amyloid fibrils (doxycycline, diflunisal). Some of them have already been approved in the EU, like tafamidis, in ATTR polyneuropathy: Tegsedi (inotersen) approved for the "treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)" and Onpattro (patisiran) for the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy".

About the product

Tafamidis is a compound that binds to TTR at the thyroxine binding sites and inhibits TTR tetramer dissociation, the rate limiting step in the amyloidogenic process. By stabilising the tetrameric native state of TTR, tafamidis increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric stabilisation effect observed with naturally occurring protective trans-suppressor variants. The result disrupts the amyloid cascade and fibril formation and interrupts disease progression.

It was first intended for the oral treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy. Then, it had been hypothesised that tafamidis would stop or slow the progression of ATTR-CM.

Tafamidis stabilised both the wild-type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Tafamidis also stabilised the TTR tetramer for 25 variants tested ex vivo, thus demonstrating TTR stabilisation of 40 amyloidogenic TTR genotypes.

The specificity of the binding to TTR also limits tafamidis to the treatment of TTR amyloidosis only, with no activity anticipated for other types of amyloidosis.

Vyndaqel 20mg (tafamidis meglumine) is already authorized in the treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. The MA granted in the EU has been approved under exceptional circumstances on the basis of completed ATTR-PN Study Fx-005 (B3461020) which was an 18-month, multicenter, randomized, double-blind, placebo-controlled phase 2/3 study that evaluated the safety and efficacy of once-daily 20 mg tafamidis meglumine in 128 patients with TTR amyloid polyneuropathy with the V30M mutation and primarily stage 1 disease. The SOB 0001 related to disease progression and long term safety in the non-Val30Met patients is assessed annually within the annual re-assessment.

In the present extension application, the indication claimed by the Applicant for VYNDAQEL 61mg (new strength, with micronized tafamidis) is the treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation.

Tafamidis is intended for chronic administration on the basis of an objective diagnosis of ATTR-CM. The recommended dose is 61 mg tafamidis orally once daily.

Efficacy was demonstrated in a multicentre, international, double-blind, placebo-controlled, randomised 3-arm study in 441 patients with wild-type or hereditary ATTR-CM, for both doses studied, 20mg and 80mg, once daily (B3461028).

A tafamidis 61 mg formulation was developed to provide a single oral dosage form for the 80 mg dose, to aid patient convenience, and claimed as bioequivalent to 4 × 20 mg tafamidis meglumine at steady-state. Thus, a dose recommendation of tafamidis 61 mg, bioequivalent to tafamidis meglumine 80 mg, is proposed for adult patients with ATTR-CM.

The dose and dosage regimen (tafamidis meglumine 20 mg or 80 mg capsules QD used in the Phase 2/3 ATTR-CM clinical program) is generally referred to throughout this document as 'tafamidis', except in those instances where the dosage or regimen were different (ie, Phase 1 studies using both tafamidis meglumine and tafamidis free acid).

The CHMP granted the following new indication within current procedure: "Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)."

Type of Application and aspects on development

Vyndaqel (tafamidis meglumine) received a Marketing Authorisation in the EU under exceptional circumstances on 16 November 2011 on the basis of completed ATTR-PN Study B3461020 (Fx 005), and is currently approved for treatment of ATTR-PN in 41 countries and is commercially available in the following 25 countries: Argentina, Austria, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Japan, Lichtenstein, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom.

The approved indication in the EU is for the 'treatment of ATTR in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment'. As a condition of approval, and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the Marketing Authorisation Holder (MAH) committed to undertake the following Specific Obligation, Follow-up Measure (FUM) 001:

Within the planned post-authorisation sub-study of the THAOS [Transthyretin Associated Amyloidosis Outcomes Survey] registry, the MAH shall evaluate in non V30M patients the effects of Vyndaqel on disease progression and its long term safety as detailed in a Committee for Medicinal Products for Human Use (CHMP)-agreed protocol, and shall provide yearly updates on the collected data within the annual re-assessment.

Vyndaqel has 2 separate Orphan Designations in the EU, covering both the approved ATTR-PN indication and the claimed targeted ATTR-CM indication:

- Familial Amyloid Polyneuropathy (TTR-FAP, now ATTR-PN) (EU/3/06/401) on 28 August 2006. At the time of designation, hereditary ATTR affected below 0.1 in 10,000 people. In 2012, the COMP confirmed that the existing orphan designation for 'treatment of TTR-FAP' includes all phenotypes of hereditary ATTR, including variant ATTR-CM, even in the absence of polyneuropathy symptoms.

- Senile systemic amyloidosis (SSA; EU/3/12/1066) on 8 November 2012. At the time of designation, ATTR wild type (previously known as SSA) affected approximately 3 in 10,000 people in the EU. It was estimated to represent for instance around 22 000 patients in France, 11 000 in Spain, 28 000 in Germany, 18 000 in Italy and 13 000 in the UK.

Several scientific advices were given to the Applicant relating to the proposed pre-clinical/clinical development programme for ATTR-CM, including the ATTR-CM phase 3 study design (B3461028) and the development of a high-dose tafamidis solid oral dosage form.

Scientific advices were also given on the pharmacokinetic comparability of a proposed high-dose tafamidis solid PO dosage form (48.8 mg tafamidis free acid capsule formulation) with 4 x 20 mg tafamidis meglumine capsules, then, on 3 exploratory relative bioavailability studies, and on a single-dose, fasted, 2-way crossover BE study comparing 61 mgA tafamidis free acid soft gelatin capsules (Test) and 4 x 20 mg tafamidis meglumine soft gelatin capsules (Reference).

A total of 377 ATTR-CM patients received tafamidis meglumine in completed/ongoing Phase 2/3 studies. In addition, 348 healthy subjects have received tafamidis (meglumine salt or free acid formulations).

The proposed indication is primarily supported by the efficacy results from a multicentre, international, double-blind, placebo-controlled, randomised 3-arm phase 3 study (B3461028) in 441 patients with wild type or hereditary ATTR-CM, assessing the 2 doses, 20mg and 80mg, once daily.

Supportive data in patients with ATTR-CM are provided from the phase 2 open-label study B3461025, its long-term extension study B3461026, and the long-term extension study B3461045 of the phase 3 study B3461028.

Pharmacology studies in healthy volunteers (ascending dose studies B3461015 and B3461040) and clinical phase 2 studies assessing PK/PD of tafamidis (B3461020, B3461021 and B3461022 in ATTR-PN, B3461025 in ATTR-CM) are provided to justify the choice of the new dose of 80mg, i.e 4x20mg of tafamidis meglumine once daily, mainly based on analysis of TTR stabilisation according to dose.

The Applicant replaced the posology of 4x20mg of tafamidis "meglumine" by a new posology with a single unit of a new soft gelatine capsule formulation with 48.8mgA of tafamidis (mgA) "free acid". Indeed, the commercial formulation, Vyndaqel, soft gelatin capsule, containing 20 mg tafamidis meglumine was considered equivalent to 12.2 milligrams of active tafamidis (mgA) free acid. Therefore, the intended high "free acid" formulation was firstly a soft gelatin capsule formulation containing 48.8 mgA tafamidis free acid (i.e 4x12.2 mgA of tafamidis (mgA) free acid equivalent to 80 mg tafamidis meglumine).

Biopharmaceutic exploratory studies assessed the BA of several tafamidis "free acid" formulations, including 1x12.2mgA, 4x12.2 mgA, 5x12.2mgA, 48.8mgA and finally 61mgA (B3461030, B3461050, B3461051, B3461052, B3461053).

Then, following results of the phase I studies, with the approval of the SAWP, it was considered that the high "free acid" formulation to be further tested should rather be a soft gelatin capsule formulation containing 61 mgA tafamidis free acid to be equivalent to 80mg tafamidis meglumine.

Lastly, 2 bioequivalence studies have been conducted to compare the new formulation of 61mgA "free acid" tafamidis and the 4x20mg tafamidis meglumine commercial formulation. Study A B3461054 was single-dose, fasted, 2-way crossover BE study comparing 61 mgA tafamidis free acid soft gelatin capsules (Test) and 4 x 20 mg tafamidis meglumine soft gelatin capsules (Reference). Study B3461056 was an open-label, randomized, 2-period, 2-sequence, crossover, multiple dose pivotal BE study in fasted healthy volunteers comparing, at steady state, 61 mgA tafamidis free acid soft gelatin capsules (Test) versus 4 × 20 mg commercial tafamidis meglumine soft gelatin capsules (Reference).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as soft capsules containing 61 mg of micronized tafamidis as active substance.

Other ingredients are:

Capsule shell: gelatine (E 441), glycerine (E 422), red iron oxide (E 172), sorbitan, sorbitol (E 420), mannitol (E 421), and purified water.

Capsule contents: macrogol 400 (E 1521), polysorbate 20 (E 432), povidone (K-value 90), and butylated hydroxytoluene (E 321).

Printing ink (Opacode white): ethyl alcohol, isopropyl alcohol, purified water, macrogol 400 (E 1521), polyvinyl acetate phthalate, propylene glycol (E 1520), titanium dioxide (E 171), and ammonium hydroxide (E 527) 28%.

The product is available in PVC/PA/Alu/PVC-Alu/PET/Paper perforated unit dose blisters.

2.2.2. Active Substance

Tafamidis meglumine, the meglumine salt form of tafamidis, is the active substance contained in the already authorised Vyndaqel 20mg soft capsules (EU/1/11/717/001-002). Tafamidis, the free acid was developed for the proposed high dose (61mg) active substance due to concentration-dependent gelling produced by the tafamidis meglumine salt in aqueous media. Full information of the active substance tafamidis free acid is provided in the dossier.

General information

The chemical name of tafamidis is 2-(3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid corresponding to the molecular formula $C_{14}H_7Cl_2NO_3$. It has a relative molecular mass of 308.12 g/mol and the following structure:

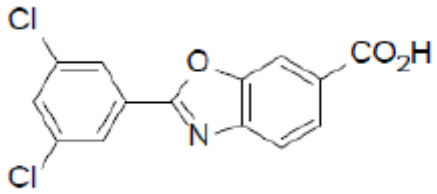


Figure 1: Active substance structure

The chemical structure of tafamidis was elucidated by a combination of mass spectroscopy, NMR analysis (^{1}H-, and ^{13}C-NMR) and FTIR.

The active substance is a non-hygroscopic white to pink powder. Solubility studies with tafamidis showed that the active substance has water solubility < 2 µg/mL at pH 5 and below.

The active substance has a non - chiral molecular structure.

While multiple polymorphs are possible for tafamidis, Form 1, the thermodynamically most stable anhydrous crystalline form under standard storage and processing conditions, is the form that has been developed and is intended for commercial manufacture.

Manufacture, characterisation and process controls

Tafamidis is synthesized in 3 main steps using well defined starting materials with acceptable specifications. The manufacturing process involves two chemical reaction steps and one recrystallization. An alternative process has been proposed to remove foreign matter by first converting it to the meglumine salt and then back to the free acid. The alternative process is not anticipated to be necessary, but if required, will be validated prior or concurrent with implementation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Changes to the manufacturing process of the active substance as a result of this extension application do not impact on the risk assessment for the presence of nitrosamine impurities. A full risk assessment for nitrosamine impurities will be undertaken for the already authorised Vyndaqel product.
Potential and actual impurities were well discussed with regards to their origin and characterised.

An enhanced development program was executed in accordance with ICH Q8 and ICH Q11. A structured quality risk management approach was employed to identify potential critical process parameters and critical material attributes based on risk of impact to the tafamidis CQAs. For each step, a combination of univariate and multivariate design of experiment (DOE) has been used, although no design space is claimed. Ranges for individual parameters were determined utilizing all the combined experimental data. The provided DOE data for Step 1 and Step 2 are identical to those submitted and approved for tafamidis meglumine. For the third step, a significant level of detail has been provided regarding its development; the proposed ranges have been properly justified.

The active substance is packaged in two sealed, low density polyethylene (LDPE) bags. The bagged material is then inserted in a high density polyethylene (HDPE) drum or equivalent secondary container. The packaging material complies with the EC 10/2011 as amended on plastic materials and articles intended to come in contact with food.

Specification

The active substance specification includes tests for appearance (visual), particle size (laser light diffraction), identification (HPLC, IR), assay (HPLC), residual solvents (GC), inorganic impurities (residue on ignition), and organic impurities (HPLC).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Microbial testing is not included on the specification for tafamidis in accordance with guidance from ICH Q6A decision tree based on the manufacturing process, inability of the finished product to support microbial growth and evidence of microbicidal nature of the active substance, routine microbial limits testing is not necessary to confirm the microbial quality of the product.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data of 14 commercial and pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 36 months at long term (25º C/60% RH) and 6 months at accelerate conditions (40º C/75% RH) according to the ICH guidelines were provided.

Supportive stability information for the active substance, manufactured at another manufacturer, by the proposed commercial process, is also provided for 1 stability batch up to 36 months at 25ºC/60% RH and 6 months at 5°C and 40ºC/75% RH.

The stability samples were evaluated for appearance, assay, degradation products, water content, and solid state form (Form 1). Results from stability studies at long term and accelerated conditions demonstrate that there are no trends in any of the measured parameters.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. The results demonstrated that the active substance was not affected by light.

Results on stress conditions under forced degradation conditions (acid, base, oxidation, thermal, and light) to confirm the suitability of the assay and purity methods to separate, quantify tafamidis and potential degradation products, and confirm that the methods are stability-indicating were also provided on 1 batch. No significant degradation was observed in the thermal/humidity solid samples or in the sample solutions exposed to hydrogen peroxide or auto-oxidation. Degradation occurred in the acid and base sample solutions heated to 40°C and 60°C, respectively. The solid tafamidis was unaffected by light exposure.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Tafamidis will be provided as a size 9.5 oblong reddish brown soft gelatin capsule filled with a white to pink coloured suspension. The capsule is printed with "VYN 61" in white.

The aim of the development of this finished product was to develop an immediate release soft gelatin capsule.

The formulation and process development of tafamidis soft gelatin capsules focused on the quality attributes defined in a Quality Target Product Profile (QTTP).

A single 80 mg tafamidis meglumine soft gelatin capsule was not technically feasible because of concentration-dependent gelling produced by the tafamidis meglumine salt in aqueous media. Several alternative salts, as well as tafamidis free acid, were evaluated. No gelling was observed with the free acid, but gelling was observed with other salts. This result is consistent with the lower solubility of the free acid under these pH conditions (6.8, 4.5, and 1.0), compared to the salt forms, which leads to lower solution concentrations of tafamidis and the absence of gel formation. Extensive experimental polymorph screening and computational predictions indicated that the anhydrous crystalline free acid Form 1 is the thermodynamically stable form at relevant storage conditions. In conclusion, the free acid form of tafamidis showed the most suitable physical and chemical properties for development of high-dose formulations. The active substance is micronized to increase dissolution rate considering the low aqueous solubility, and for better control over particle size distribution and uniformity for

manufacturing. Particle size specifications have been established based on the consistency of the manufacturing process and experience with the active substance.

The excipients were selected based on the need to have a water-dispersible suspension to achieve an acceptable dissolution profile. The compatibility of the selected excipients with the active substance is based on stability data of the finished product, which is acceptable. The main excipients selected are well established, common for this type of formulations, are described in Ph. Eur. except the ink which is of in house standard and their functions and amounts are well described. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The development approach is based on an understanding of the relationships between formulation inputs and process parameters on the critical quality attributes (CQAs) of the finished product.

A risk assessment was performed based upon prior knowledge (including literature and platform understanding), as well as the knowledge that had been gained during the transfer of the manufacturing process.

Once the proposed commercial formulation and manufacturing process for the finished product was established, an understanding of the relationships between the finished product quality attributes identified in the QTPP and the materials and processing parameters used in manufacture was developed. A risk assessment was conducted to highlight those process parameters which could potentially have an impact on finished product quality attributes.

The control strategy for the finished product consists of control of material attributes, control of the critical process parameters, critical in process controls and release testing.

Formulation development for the tafamidis capsule was based on the previous knowledge of the tafamidis meglumine capsule fill composition. The option to use the same fill formula was quickly ruled out as the tafamidis rapidly agglomerated and separated from the bulk liquid fill. Exploratory dissolution testing also proved to be slow.

A suspension-filled capsule was therefore targeted for development. For the liquid suspension formulation, the following was desired: a base excipient that readily dispersed in aqueous media, a surfactant to promote dispersion and dissolution of the active substance in the formulation, a viscosity-enhancing agent to promote suspension homogeneity during manufacture, and an antioxidant to minimize the risk of oxidative degradation and gelatin cross-linking.

PEG 400 was chosen as the water miscible liquid base because it promotes rapid dispersion of tafamidis suspension following mixing with aqueous media, and it is a commonly used component of soft gelatin capsule formulations. Polysorbate 20 was selected as the surfactant based on the degree to which it is miscible with PEG 400 and able to maintain a homogeneous bulk fill. In combination, PEG 400 and polysorbate 20 constitute a base to which other excipients were added and assessed separately in prototypes manufactured exclusively for stability. Povidone K-90 was included to enhance viscosity in PEG-based liquids and reduce settling during manufacture. Based on the outcome of the stability testing and extensive use in products globally, BHT was selected as the antioxidant for the proposed commercial product.

Studies describing the development of the dissolution method were presented. There are two proposed dissolution mediums (Tier 1 and Tier 2).Tier 2 medium will only be used when the presence of gelatin shell pellicle formation is observed. However, the CHMP recommends withdrawing Tier 2 medium when more stability results will allow confirming the absence of crosslinking. The discriminatory power of the dissolution method was investigated using capsules filled with suspensions made with active substance of different particle size (milled and unmilled active substance). The dissolution profiles are presented

and the f2 similarity comparison for these two profiles demonstrated the profiles are not similar, thus supporting the discriminatory capacity of the dissolution method for a relatively small difference in active substance particle size. The discriminatory power of the dissolution method was also tested against variant capsule formulations prepared with the intention of disrupting the ability of the drug to readily disperse. Again, results support the discriminatory power of the dissolution method.

The finished product is a soft capsule for which the same typical equipment (mixer homogenizer, encapsulator, a tumbler dryer followed by tray drying in a tunnel) and scale as the currently authorised Vyndaqel 20 mg are used providing a strong basis of knowledge for the development strategy. An overall quality risk management approach was employed to identify potentially critical process parameters (raw materials, homogenizer speed, mixing time, deaeration time, gelatin mass age, capsule fill weight, tumble dry cycle, number of capsules on tray, in process fill moisture, washing cycle, packaging) and assess their impact on the finished product quality attributes (appearance, identity, assay, uniformity of dose, dissolution, impurities, fill moisture, stability).

The primary packaging is PVC/PA/Alu/PVC-Alu/PET/Paper perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 9 main steps: mixing, homogenizing, deaerating, in-line printing, encapsulation, drying, washing, drying, and packaging. The process is a standard manufacturing process.

Critical step of the process are encapsulation and capsule drying. Associated in-process controls were described.

The manufacturing process used to manufacture the registration batches is a standard process for the manufacture of soft gelatin capsules. Therefore, validation on production scale batches will be completed prior to release of the product for commercial use. The in-process controls are adequate for this type of manufacturing.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form appearance (visual), identification (HPLC, UV), assay (HPLC), content uniformity (Ph. Eur.), degradation products (HPLC), dissolution (Ph, Eur.), capsule fill moisture (KF), BHT assay (HPLC), and microbial limits (Ph. Eur.).

There is no degradation observed during manufacture and stability of the finished product. Therefore, there is no specified degradant in the finished product specification. The limit established for unspecified degradation products is consistent with ICH Q3A. A total degradation product acceptance criterion has been established. Analysis of the batches indicated that all batches met the acceptance criteria.

Analysis of the batches revealed no unspecified unidentified impurities exceeding the identification threshold, for a maximum daily dose of 61 mg.

An elemental impurities risk assessment was performed on the finished product. Based on the data, no controls or acceptance criteria for individual elemental impurities are proposed, as the risk of elemental impurities being present at levels above their PDEs has been established to be negligible by the risk assessment process and supporting analytical data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. There are no additional reference standards or materials used for testing of the finished product.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing,

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 12 months under long term conditions (30° C/75% RH and 25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are representative to those proposed for marketing, but the packaging is different from the commercial one (3-ply blister material whereas, a 4-ply blister material and peel/push lidding was selected for the commercial blister). As the stability packaging has been demonstrated equivalent to the commercial one, no additional stability data were provided with the commercial packaging. As post approval stability protocol and stability commitment, the applicant commits to inform the competent authorities of any out of specification stability results for Vyndaqel 61 mg capsules packaged in the proposed commercial packaging.

Samples were tested for appearance, assay, degradation impurities, BHT, dissolution, capsule fill moisture content, and microbial limits. The analytical procedures used are stability indicating. The data from the primary stability study demonstrates that there are no significant trends in any of the measured parameters.

A photostability study in 3 batches was carried out according to the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products. All parameters measured for the confirmatory photostability study met the specifications. No significant difference was noted between the initial results, control and exposed samples. Therefore, it is concluded that the finished product is stable to light and no precautionary packaging or labelling is required with respect to light.

To determine the effect of extreme temperature variation, one representative batch was cycled through -20°C for four days followed by 40° C for four days. A second cycle was then performed for -20°C for three days followed by 40° C for three days, prior to the samples being tested. The results from the thermal cycling study from one representative batch showed that fluctuations in temperatures from -20 ° C to 40° C over two cycles for a total of 1 week at each condition, did not affect any of the capsule quality parameters evaluated.

Forced degradation experiments were performed to establish the extent and nature of potential degradation pathways and to confirm the suitability of the HPLC assay and purity method. The experiments included thermal, thermal humidity, and photolysis studies. Data showed no degradation and good mass balance within analytical variability.

Based on available stability data, the proposed shelf-life of 24 months without any special conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance and finished product

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To withdraw Tier 2 medium when more stability results will allow confirming the absence of crosslinking

2.3. Nonclinical aspects

2.3.1. Introduction

This Line Extension application introduces a new indication (ATTR-CM) with a new human recommended dose (61 mg QD), including replacement by a different salt (tafamidis free acid). Only few modifications have been made in the submitted nonclinical package in comparison of the nonclinical package previously authorised in MAA for treatment of ATTR-PN. In order to detail,

- regarding drug substance modification, the original MA was obtained with tafamidis meglumine as active substance. Tafamidis meglumine, is the meglumine salt form of tafamidis free acid, the only active ingredient contained in tafamidis meglumine. The nonclinical studies have been performed with both tafamidis meglumine or tafamidis free acid and were contributive to the toxicological profile for both tafamidis forms (salt or free acid).

- regarding drug product modification, since the current MAA is requested for tafamidis free acid, a new formulation is developed in order to obtain soft capsules, same as in the previous MAA, however, the excipients are different. The final formulation has not been assessed in nonclinical studies, it is acceptable since the used excipients are usual and does not raise any specific concerns.

- regarding the new indication (ATTR-CM), there are no new primary pharmacodynamics (PD) studies since the time of the current Vyndaqel MA and subsequent variations. Tafamidis is as a specific stabilizer of transthyretin (ATTR) tetramer and has been developed in ATTR-PN and ATTR-CM. In vitro data with tafamidis meglumine and/or tafamidis free acid have been reported to decrease fibril formation of WT, and amyloidogenic mutants of TTR (variant forms of the ATTR-PN form and variant forms of ATTR-CM)

and no relevant animal disease model to evaluate TTR stabilizers were available. The absence of new studies is acceptable.

- finally, regarding the recommended dose increase, the Applicant has reviewed every calculated margin of exposure or safety margins since at a clinical dose of 20 mg/day tafamidis meglumine the measured steady state mean human C_{max} and AUC_{24} are 2.66 µg/mL and 49.6 µg•h/mL respectively and at a clinical dose of 61 mg/day tafamidis, the steady state mean human C_{max} and AUC_{24} are 8.55 µg/mL and 170 µg •h/mL respectively. Consequently, the Applicant has modified the SPC according to these new lower safety margins. There are no safety margins for liver effects at the new clinical recommended 61 mg tafamidis free acid and the SPC section 5.3 was therefore updated.

Since the time of the MA and subsequent variations, a total of 11 new nonclinical studies were conducted and have been reported in the nonclinical package. Only these 11 new studies are presented in this report and the previous overviews of pharmacology, pharmacokinetic, and toxicology are updated with the 11 new studies and the lower safety margins.

2.3.2. Pharmacology

No new primary pharmacodynamic studies since the time of the current Vyndaqel MA and subsequent variations are provided.

Familial amyloidosis, the most frequently inherited amyloidosis, is caused by an accumulation of insoluble fibrillar proteins (amyloid) in the tissues in sufficient amount to impair normal functioning. The two major phenotypes include transthyretin amyloid polyneuropathy (also known as familial amyloid polyneuropathy, or ATTR-PN), primarily affecting the peripheral nerves and TTR amyloid cardiomyopathy, (also known as familial amyloid cardiomyopathy or ATTR-CM when associated with variant TTR, or senile systemic amyloidosis or SSA when associated with wild-type TTR) primarily affecting the myocardium.

TTR is a transport protein for thyroxine (T4) and retinol-binding protein-retinol complex. It is secreted by the liver as homotetramers and is present in this form in plasma. By binding to both tetrameric wild-type and amyloidogenic variants of TTR, tafamidis inhibits tetramer dissociation, the rate limiting step in the formation of TTR amyloid, thereby disrupting the progression of ATTR.

Tafamidis free acid binds to TTR with negative cooperativity with dissociation constants of 2-3 nM (Kd1) and 154-278 nM (Kd2) and with a stoichiometry of 0.81 ± 0.02 thus demonstrating specificity to TTR over all other plasma protein. Under physiological conditions, tafamidis free acid almost completely stabilized tetramer dissociation at a concentration Tafamidis:TTR of 1.5. Under acidic conditions that induce fibril formation, tafamidis free acid stabilized wild-type TTR and the two disease-related TTR variants V30M and V122I and prevented fibril formation with an EC50 of the order of TTR physiological concentration. TTR tetramers dissociate into unfolded monomers in the presence of urea, thus preventing their reassociation into a tetramer. Under urea denaturation conditions, tafamidis meglumine and free acid stabilized in a concentration-dependant manner TTR tetramers in plasma of normal individuals, V30M or V122I mutation-carrying patients. Tafamidis was also shown to be effective in the stabilization of 26 other TTR variants.

The Applicant submitted only in vitro primary pharmacodynamics studies. The absence of in vivo studies is acceptable since no validated model of ATTR disease was available at the time of nonclinical development.

The binding selectivity of tafamidis was investigated. In an assay testing the binding of tafamidis to more than 50 enzymes or receptors, tafamidis free acid was found to notably bind to δ-2 opioid receptor with an IC50 of 8.3 µM. It exerted a concentration-dependant agonistic activity. There is a possible

mechanistic link between agonism of δ-2 opioid receptors and the dose-related emesis observed in the dog, it was demonstrated that it only happens at supra-clinical, and therefore nonrelevant, doses of tafamidis. NSAIDs are known to bind to TTR. Specific assays were conducted to know if tafamidis meglumine also shares their COX-inhibiting properties. The results showed no significant inhibition of COX-1 or COX-2 activities. This is consistent with the outcome of the in vitro receptor and enzyme binding assay. Furthermore, it is expected that tafamidis will preferentially bind to TTR, even in the presence of diflunisal or diclofenac, and that no significant pharmacodynamic drug interaction would be observed.

Regarding safety pharmacology, tafamidis underwent the core battery studies. Tafamidis meglumine was tested for its effects on CNS in an acute neurotoxicity study in rats. Tafamidis meglumine induced no adverse neurological effects up to 100 mg/kg. In vivo, no changes in respiratory, body temperature, or blood gases were recorded in telemetered dogs up to 300 mg/kg. Regarding effects on cardiovascular system, no effects on heart rate or hemodynamic parameters were found in conscious telemetered dogs administered up to 300 mg/kg. However, a dose-dependent stimulation of Ikr current attaining up to 9.3% at 30 µM was detected in vitro. In vivo, dog electrocardiograms showed a prolongation of QRS interval (3% and 6% at 100 and 300 mg/kg respectively) and a shortening of QTc interval (3% to 6% at 100 mg/kg and 4 to 6% at 300 mg/kg). However, given the severity of the disease and since no concern arose from clinical assessment, it could be considered that the benefit/risk ratio is favourable.

2.3.3. Pharmacokinetics

Eight new in vitro DDI studies were presented by the Applicant in this current MAA. Therefore, PK overview has been updated with these new data.

Absorption

In in vitro studies, tafamidis meglumine was well absorbed through transcellular transport. It was not a substrate of OAT, OCT, MRP2 or P-gp transporters but it showed an inhibitory effect on the OATP and/or BCRP and MRP transporters while a slight inhibition was observed on P-gp transporter at higher concentrations. In vivo, different vehicles were used during preclinical development. After single administration, exposure was greater when tafamidis meglumine was formulated as a solution in 7.5% Vitamin TGPS instead of a suspension in 0.5% CMC in rats and in dogs. Food seems to decrease exposure to tafamidis in non-fasted rats. The bioavailability was complete or almost complete (108% in rats and 91% in dogs) based on 24-hour studies. Plasmatic half-life is 29-43 hours in rats and 55-62 hours in dogs. Distribution volumes were small (316 mL/kg in rats and 317 mL/kg in dogs) and correspond to extracellular water content. Repeated dose studies showed saturation of absorption in dogs and accumulation in mice, rats and dogs after repeated dosing.

Distribution

Tafamidis is widely distributed in rats. The highest concentrations were found in harderian glands, stomach and liver. After 168 hours, tafamidis was still present in a majority of tissues. Regarding protein binding, in vitro studies determined a percentage of binding of 97.1% in mice, 99.0%in rats, 99.1% in dogs and 99.2% in humans. Binding to human plasma is predominantly due to significantly binding to the HSA component (>99.6% with Human Serum Albumin and 12% with α-1-Acid Glycoprotein). Distribution in blood cells revealed that it is not particularly associated with blood cells. Tafamidis crosses the placental barrier, rat fetuses receiving to up 4% of the administered dose to the dams.

Metabolism

In vitro, tafamidis was not readily metabolised by rat, dog or human S9 and was stable in presence of mouse, rat, rabbit, dog and human hepatic microsomes, 94% of unchanged tafamidis remaining at the end of incubation. In vivo, tafamidis plasma metabolism was studied in mice, rats, rabbits, dogs and humans. The metabolism was not extensive. Three metabolic pathways are proposed: glucuronidation mediated by UGT (mainly 1A9, 1A1 and 1A3 and in a minor extent 1A6, 1A7, 1A8 and 2B7), sulphation and oxidation. In humans, the only metabolite was acylglucuronide. Acylglucuronide metabolite was also the major metabolite in all tested species excepting in rabbits where the only metabolite was the monoxide also found in mice. The dog showed a sulphate conjugate not found in any other species. Acylglucuronides have been increasingly identified as reactive electrophilic metabolites, capable of undergoing intermolecular reactions with proteins leading to covalent drug-protein adducts, initiating toxicity/immune responses, the liver being the target organ (Bailey and Dickinson, 2003; Skonberg et al, 2008).

Tafamidis did not significantly inhibit CYP2C9/19, 1A2, 2D6 and 3A4. It showed an inhibitory effect on CYP2C8. Tafamidis induced CYP3A4 in cryopreserved human hepatocyte cultures from female donors but not from males. This effect is minimal in presence of albumin.

Excretion

Excretion is slow: only 88% of the administered dose is excreted after 168 hours. Mass balance studies with cannulated rats showed that tafamidis is subjected to enterohepatic recycling. The main excretion route is the bile (~48%) while feces represents 21-24% of total excretion and urine 19-21%. Renal elimination of tafamidis as parent compound is low, the major urinary metabolite being the acylglucuronide. Tafamidis is excreted in milk and is systemically absorbed by pups from the gastrointestinal tract.

Pharmacokinetic drug interactions

The potential for tafamidis to cause enzyme-mediated DDI from systemic inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 is unlikely. Tafamidis may inhibit the intestinal activities of UGT1A1. Tafamidis did not induce CYP1A2, but did induce CYP2B6 and CYP3A4, however 20 mg tafamidis meglumine did not significantly affect the pharmacokinetics of midazolam in humans. Based on these negative CYP3A4 induction results, it can also be concluded that the likelihood of CYP2B6 clinical induction is low. The potential for tafamidis to cause transporter-mediated DDI by inhibiting MDR1 (P-gp) (systemically and in the GI tract), OCT2, OATP1B1, OATP1B3, MATE1, and MATE2K is unlikely. However, tafamidis has the potential to inhibit BCRP (systemically and in the GI tract), OAT1, and OAT3 at clinically relevant concentrations. Additional DDI risk assessments were performed for BCRP, OAT1, and OAT3 inhibition using mechanistic static models to estimate the maximal increase in AUC of substrates of these transporters when co-administered with tafamidis. The maximal increase in the plasma AUC of rosuvastatin due to inhibition of BCRP in the GI tract is estimated to be 92% when dosed with 20 mg/day tafamidis meglumine and 98% when dosed with 61 mg/day tafamidis free acid. The maximal estimated increase in AUC of OAT1 and OAT3 substrates was determined to be less than 25% for both the 20 mg/day tafamidis meglumine and 61 mg/day tafamidis free acid doses. The potential interactions of tafamidis at clinically relevant concentrations are reflected in the SPC. In conclusion, pharmacokinetic data support the use of tafamidis for the treatment of transthyretin amyloidosis in adult patients with wild type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalization.

2.3.4. Toxicology

Three new in vitro genotoxicity studies on starting material/impurity were presented by the Applicant in this current MAA. Therefore, toxicology overview has been updated with these new data.

Single dose toxicity was assessed only in dogs. No mortality or serious adverse effects were observed up to 600 mg/kg. The acute oral toxicity of tafamidis in dogs can be considered as low.

In repeat dose toxicity studies, tafamidis was tested in mice up to 28 days, in rats up to 26 weeks and in dogs up to 39 weeks. At high doses, tafamidis caused mortality in mice, rats, and dogs. Target organs identified in these studies included liver, kidney, and gastrointestinal tract. Other findings related to administration of tafamidis included clinical observations (some indicative of an effect on the CNS) and effects on clinical pathology parameters, lymphoid tissues, bone marrow, and heart.

Stomach necrosis and distension in rats and emesis and abnormal faeces in dogs were observed.

The liver appeared as target organ for toxicity in the different species tested (increased liver weight and increased total bilirubin in rats and dogs associated with some changes in liver enzymes). The mechanism has not been determined. However, the hepatic findings were observed at safety margins >3 for 20 mg of tafamidis meglumine and ≥0.7 for 61 mg of tafamidis free acid. These findings are monitorable via standard clinic endpoints and have generally been shown to be reversible. Given the available clinical data from patients treated with the 61 mg dose of tafamidis, the safety margins were updated, and in light of these new safety margins, no safety margin was able to be defined for liver effects and this the only relevant finding requiring an update of Section 5.3 of the SmPC (see comment on SPC section 5.3).

Renal nephrosis was observed in male Tg.rasH2 mice with a higher incidence and severity at 90 mg/kg/day and not observed at ≤30 mg/kg/day, with corresponding AUC_{24} values, which were ≤9.6x and ≤2.8x the human steady state AUC_{24} at clinical doses of 20 mg tafamidis meglumine and 61 mg tafamidis, respectively. These findings are monitorable via standard clinic endpoints and have generally been shown to be reversible.

Lymphoid depletion, especially thymus depletion and atrophy was shown in rodents. Red blood cells parameters were decreased in rats whereas they were increased in dogs. In female animals, tafamidis induced estrous disruption in mice, increased ovaries and uterus weight in rats, but decreased ovaries weight in dogs. The NOEL was 10 mg/kg in mice and the NOAELs were 30 mg/kg in rats and 45 mg/kg in dogs.

Tafamidis underwent the conventional genotoxicity battery. The Ames test and the micronucleus rat were negative. In the chromosomal aberration assay, a dose-dependent increase of polyploidy was observed in the presence of S9.

No carcinogenic potential was observed in transgenic rasH2 mice treated up to 90 mg/kg for 26 weeks and in Sprague-Dawley rats up to 30 mg/kg for 2-years. General signs of toxicity consisting in hepatic and renal lesions in mice and in rats and these finding are consistent with those seen previously in toxicity studies.

The fertility study did not reveal any concern regarding reproductive toxicity in males or in females. In rats, tafamidis induced maternotoxicity (mortality at 45 mg/kg, decreased body weight at 30 mg/kg). It showed foetotoxicity at ≥30 mg/kg (decreased body weight). It was not teratogenic.

In rabbits, tafamidis induced maternotoxicity at low doses: at ≥2 mg/kg, reduced body weight gain was shown and at 8 mg/kg, two does aborted and were subsequently sacrificed. In the 8 mg/kg group, the number of late resorptions was increased. Regarding development, skeletal abnormalities were seen at ≥2 mg/kg and the number of foetuses and litters with any alteration was increased. They mainly consisted in head and eye abnormalities seen in 3 foetuses from 2 litters.

In the peri- and postnatal study, tafamidis induced mortality in F0 dams at 15 mg/kg and higher. The dams of the 30 mg/kg high dose group were sacrificed because there were no surviving pups in 20 litters out of 25. In the F1 generation, all pups of the high dose group died between PND 1 to 4and 2 pups of the mid dose group died during the post-weaning period and had lower body weight. Pups from the mid-dose group also showed head and eye abnormalities, retardation in male sexual maturation and decreased learning performance. The F1 generation had no alteration of mating or reproductive performance, but F2 generation had lower foetal body weight and rotated limbs.

Tafamidis was not phototoxic in a study in pigmented rats and did not affect T-cell dependent antibody responses (TDAR) in mice. A synthetic starting material and 2 potential impurities were not mutagenic in bacterial assays.

2.3.5. Ecotoxicity/environmental risk assessment

A new ERA is submitted by this Applicant according to the current guideline since the environment exposure will increase with a higher population exposure (new indication and higher posology). Fpen refinement is different with addition of the second indication (more patients affected in ATTR-CM) and consequently the calculated PEC increase. Moreover, the higher posology conducted also at a higher PECsw. As a result, the Applicant highlighted that PECsw reached the PEC action limit of 0.01 µg/L. No phase II data have been provided; however the Applicant has already planned a phase II tier A and will be available 4Q 2020. This proposed approach and timetable are acceptable.

2.3.6. Discussion on non-clinical aspects

Since the time of the MA for ATTR-PN indication and subsequent variations, a total of 11 new non-clinical studies were conducted and have been reported in the nonclinical package. These new studies revealed no special hazard for humans.

GLP

All pivotal studies in the original non-clinical package were GLP-compliant. For the 11 new studies, the 8 in vitro DDI studies were not GLP-compliant, and 3 genotoxicity studies with impurities were GLP-compliant. This was considered acceptable.

Regarding the recommended dose increase in the new agreed indication (20 mg tafamidis meglumine to 61 mg tafamidis free acid), the applicant has updated PK parameters collected in clinical trials in patients treated by 61 mg tafamidis free acid. The safety margins cited in section 5.3 of the SmPC of Vyndaqel 61 mg were therefore updated (compared to these cited in section 5.3 of Vyndaqel 20 mg). There is no safety margin for liver effects in different species tested and for reprotoxicity in rats and rabbits. The updated wording of section 5.3 of the SmPC has reflected this new absence of safety margin.

2.3.7. Conclusion on the non-clinical aspects

It is considered that the toxicological package available with tafamidis supports the marketing authorization of Vyndaqel for the proposed indication (ATTR-CM).

The wording of the section 5.3 of the SmPC for Vyndaquel 61 mg meglumine reflects the absence of the safety margins for liver effects in different species tested and for reprotoxicity in rats and rabbits.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP inspection has been adopted for the clinical study B3461028. The outcome of this inspection and the satisfactory responses to its findings were an integral part of this procedure and have been provided by Day 181. The study was considered GCP – compliant.

- ***Tabular overview of clinical studies***

Study ID	No. of study centres / locations	Design	Study Posology	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Patient Population	Primary Endpoint
B3461028	60 centers International	Phase 3, double-blind, randomized, placebo-controlled study in patients with ATTR-CM	Tafamidis 20 mg or 80 mg QD or placebo	20 mg:88 ent / 60 compl 80 mg:176 ent / 113 compl Placebo: 177 ent / 85 compl	30 months	Tafamidis group: 241 male and 23 female, 75.0 years (46-88) Placebo group: 157 male and 20 female, 74.0 years (51-89)	ATTR-CM variant or wild type	All-cause mortality and frequency of CV-related hospitalisations
B3461045	41 centers International	Randomised, extension	Tafamidis 20 mg or 80 mg QD	252 enrolled, 219 ongoing	60 months	Tafamidis group: 221 male and 21 female, 77.0 years (54-91)	ATTR-CM variant or wild type	Long-term safety (including all-cause mortality)
Fx1B-201 (B3461025) Previously submitted	6 centers USA	Open-label	Tafamidis 20 mg QD	35 patients enrolled, 32 complete	12 months	3 female, 32 male 76.3 years (68.1-86.5)	ATTR-CM variant or wild type	TTR stabilisation at Week 6 (primary) and at Months 6 and 12 (secondary)
Fx1B-303 (B3461026)	5 centers USA	Open-label extension	Tafamidis 20 mg QD	31 patients enrolled, 5 ongoing	10 years	3 female, 28 male 77.7 years (69.23-87.64)	ATTR-CM variant or wild type	Long-term safety. Clinical endpoints included patient global assessment, 6MWT, markers of cardiac function (eg, echocardiograms, quality of life measures).

2.4.2. Pharmacokinetics

Absorption

Absorption

Bioavailability

No study was performed on Tafamidis free acid absolute bioavailability.

Bioequivalence

Bioequivalence of Tafamidis free acid, and particularly the 61 mg free acid capsule, compared to the commercial 20 mg Tafamidis meglumine (at the dose of 80 mg) was explored in Studies B3460154 (single dose fast and fed state) and B3461056 (multiple doses, fasted state).

Comparing the two treatments in Study B3461054 after a single dose in fasted state, there was underexposition with 61mg Tafamidis free acid (0.80 fold for Cmax) compared to 80 mg Tafamidis meglumine. In fed state there was overexposition with 61mg Tafamidis free acid (1.21 and 1.24 fold for AUClast and Cmax) compared to 80 mg Tafamidis meglumine.

At steady state under fasted condition, however, with Study B3461056, bioequivalence could be proven between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine.

Bioequivalence between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine was proven at steady state (fasted). However, it could not be proven after single dose, which is the most relevant and discriminant according to the guideline for evaluation of bioequivalence. Therefore, it cannot be considered that bioequivalence has strictly been proven (and this term should be taken off in the SmPC), which is a serious concern since most efficacy data come from 4*20 mg Tafamidis meglumine treatments. Please refer to the B/R discussion for relevance of this non-bioequivalence on benefit-risk.

The applicant justified why steady state conditions are the most relevant here. They acknowledged that bioequivalence has not been proven, but in the context, changes in exposure, and higher Cmax in particular, are not expected to be relevant.

Influence of food

Assessing food effect for both treatments, for the 61 mg Tafamidis free acid, there was over-exposition in fed state (1.32 fold for Cmax), and for the 80 mg Tafamidis meglumine there was under-exposition in fed state (0.85 fold for Cmax). AUCs were never impacted by food effect.

B3461054 study was a single-dose cross-over relative bioavailability study under fasted and fed conditions. One objective of this study was to estimate the effect of food on the once daily tafamidis 61 mg formulation. The relative bioavailability (90% CI) of tafamidis 61 mg fed compared to fasted were 106.10% (98.40%, 114.39%), 108.10% (101.71%, 114.88%) and 132.41% (121.02%, 144.87%) for AUCinf, AUClast and Cmax, respectively. Therefore, co-administration of tafamidis 61 mg with a meal demonstrated increases in AUCinf (6%) and Cmax (32%).

Simulations using the population PK model suggest the difference in steady-state Cmax under fed conditions is <10% compared to fasted conditions, which is considered not to be clinically meaningful (Study Report PMAR-EQDDB346aOther-452).

All Phase 2/3 efficacy and safety trials with tafamidis meglumine and tafamidis formulations have been performed without regard to meals. Given the clinically unimportant differences in exposure under fed conditions, no dosage adjustments or time restrictions between meal and drug intake are necessary.

Regarding food effect, the scientific advice accepted that the multiple dose study could be performed under fasted condition, however it also noted that "If a significant food effect will be detected for the 61 mgA tafamidis free acid formulation, it might be necessary to adapt the method of administration wording in the SmPC from can be "taken with or without food" to "to be taken on empty stomach".

The CHMP agreed that the wording of the method of administration of tafamidis 61 mg in section 4.2 of the SmPC is "taken with or without food".

Distribution

Tafamidis is highly protein bound (>99%) in plasma. The binding of tafamidis (10 µM or 3.08 µg/mL) to human serum albumin or α1-Acid Glycoprotein is >99.6% and 12%, respectively. Tafamidis binds to albumin with a dissociation constant (Kd) of 2.1 to 2.5 µM or 0.65 to 0.77 µg/mL.

The apparent steady-state volume of distribution for tafamidis meglumine is approximately 16 L (11.5 L central compartment and 4.51 L peripheral compartment).

Elimination

Based on population PK results, the mean steady-state half-life is approximately 49 hours, and the apparent oral clearance of tafamidis meglumine is 0.228 L/h

Excretion

The results from the human mass balance study (B3461017 [Fx1A- 107] Report Body Section 11.4) indicated that faecal excretion represented the major pathway for elimination with mean faecal recovery accounting for 58.5% of the total dose administered versus 22.4% recovered in urine. This is consistent with nonclinical data which demonstrated biliary excretion and evidence of enterohepatic recycling.

Most of the radioactivity in plasma and faeces was accounted for by unchanged parent drug, tafamidis, while in urine the major radiolabeled compound was a glucuronide metabolite.

Metabolism

In vitro and in vivo studies indicate that tafamidis is metabolized by glucuronidation to an acylglucuronide (Studies 400477, 401242, 400699, 400553, and 401485). Given the predicted lack of reactivity for tafamidis acylglucuronide relative to other structural motifs, the low extent of metabolism through this pathway, the low incidence of events that could represent hypersensitivity reactions, the clinical relevance of this potential toxic mechanism seems low. The Phase II conjugating enzymes uridine 5'- diphospho-glucuronosyltransferase (UGT) 1A9, UGT 1A1, and UGT 1A3 appear to be the major isoforms responsible for the formation of the acylglucuronide, while minor activity was observed with UGT isoforms 1A6, 1A7, 1A8, and 2B7 (Study 401242).

Interconversion, PK of metabolites, and consequences of possible genetic polymorphism

Not applicable, this was discussed in the first application.

Dose proportionality and time dependencies

Dose proportionality and time dependency of tafamidis free acid was not explored, the applicant should discuss if changes in absorption with the free acid could occur at different dose, or if the changes in absorption with the free acid impact time dependency.

Intra and inter-subject variability

Variability for AUCtau and Cmax, based on %CV ranged from 18% to 23% for both formulations. Intrasubject variability for the free acid form has not been explored.

PK in target population

Population PK modelling (described afterwards) showed that steady state exposure change for patients with ATTR-PN compared to healthy volunteers and patients with ATTR-CM was less than 10%.

Special populations

- Impaired renal function: The effects of creatinine clearance on tafamidis PK were evaluated in the population PK analysis (Report PMAR-EQDD-B346a-Other-452); PK estimates indicated no difference in steady-state clearance of tafamidis in patients with creatinine clearance <80 mL/min compared to those with creatinine clearance >80 mL/min. Therefore, no dosage adjustment is necessary for patients with renal impairment.
- Impaired hepatic function: Study Fx1A-105 (B3461016) evaluated the PK of tafamidis meglumine in subjects with mild or moderate hepatic impairment. Subjects with severe hepatic impairment were not evaluated. Based on these data and previously known PK of tafamidis, no dosage adjustment is necessary for patients with mild and moderate hepatic impairment. No data are available in patients with severe hepatic impairment.
- Gender: Based on population PK results, the pharmacokinetics of tafamidis were not significantly affected by gender. This is consistent with Study B3461018 that demonstrated similarity in the observed noncompartmental PK parameters between males and females.
- Race: Based on population PK results, the PK of tafamidis were not significantly affected by race. Study B3461009 evaluated the PK of tafamidis meglumine in Japanese and Western healthy volunteers but no statistical comparison was performed.
- Weight: In the population Pk modelling, Body weight was a structural covariate in the model as exponents for CL/F, Vc/F, Q/F and Vp/F. The estimates were 0.618 for CL/F and Q/F, and 0.545 for Vc/F and Vp/F. However, the effect of body weight on tafamidis steady-state exposure was less than 20% and clinically not meaningful.
- Elderly: Based on population PK results, subjects above 65 years had an average 15% lower estimate of Tafamidis clearance at steady-state compared to subjects <65 years. This difference in clearance results in <20% increases in mean Cmax and AUC compared to younger subjects and is not clinically significant. Therefore, no dosage adjustment is necessary in subjects above 65 years.
- Children: There is no relevant use of Tafamidis in the paediatric population.

Exposure relevant for safety evaluation

The most relevant data for exposure for safety evaluation are from steady state after 61 mg tafamidis free acid QD:

- Cmax,ss : 8.553 microg :mL (CV 23%),
- AUCtau,ss : 170 microg.h/mL (CV 23%).

2.4.3. Pharmacodynamics

Mechanism of action and Primary pharmacology (from initial application in ATTR-PN):

Tafamidis meglumine is a novel, specific stabilizer of tetrameric wild-type and amyloidogenic TTR that binds to the native tetrameric form of TTR and thereby inhibits tetramer dissociation and TTR amyloid formation. This novel class of TTR stabilizer drug has the potential to slow the progression of ATTR.

Dissociation of the TTR tetramer to monomers is the rate limiting step in the pathogenesis of TTR amyloidosis. The folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments, and ultimately, amyloid fibrils. All disease-associated mutations characterized thus far destabilize the TTR tetramer and many influence the velocity of rate-limiting tetramer dissociation.

A proprietary stabilisation assay has been developed and validated by the Applicant to directly determine the effects of tafamidis in plasma samples from patients receiving tafamidis. The method is based on the determination of the abundance of the tetrameric form of TTR, measured by immunoturbidimetry, after a 2-day denaturation in 4.8 M urea. The denaturation of TTR in urea requires the dissociation of the tetramer to the monomer. Therefore, in urea, the abundance of the tetrameric form of TTR is directly linked to the rate of tetramer dissociation and the stability of the TTR fold.

The TTR stabilisation was calculated as follows: the fraction of initial tetramer concentration was calculated before and after treatment (FOI dosed) with tafamidis at different timepoints. The percent stabilisation of TTR tetramer is defined as follows:

Percent stabilisation = [average FOIdosed – average FOIbaseline]/ average FOIbaseline x 100.

Consequently, a percent stabilisation value of 100% has a two-fold increase in the fraction of initial value over baseline and a percent stabilisation of 200% has a three-fold increase in the fraction of initial value over baseline.

The main results on TTR stabilisation were presented in study after single and repeated administration of tafamidis (Fx-002):

The percent of TTR stabilisation varies with the average concentration of tafamidis at Tmax. The dose selection is based on the demonstration that a plateau is reached from TTR stabilisation (with range of differences from baseline:117-234), determining a tafamidis:TTR stoichiometry of 1.2-1.4.

Based on single-dose PK data extrapolated to steady-state for tafamidis a dose of 20 mg tafamidis per day corresponds to a range of tafamidis:TTR stoichiometry of 1.2 to 2 which is compatible with TTR stabilisation.

The selection of 20 mg as the therapeutic dose relies on an extrapolation from other doses, based on the linearity demonstrated for tafamidis for doses between 15 and 30 mg, as no data after repeated administration of 20 mg tafamidis were generated.

Secondary pharmacology

QTc prolongation: No inhibition of the hERG potassium channel current in transfected human kidney embryo 293 cells was observed at tafamidis concentrations of 1, 3, 10 and 30 µM. No effect on QTc interval prolongation was observed when a supra-therapeutic, single dose of 400 mg tafamidis meglumine was administered to healthy volunteers in study B3461031.

NT-proBNP: this a cardiac biomarker has been used in study B3461028 firstly to select patient population, then to try to analyse efficacy results and find a difference between the 2 tested doses (see effccacy part).

Genetic differences in PD response

Tafamidis stabilized both the wild-type TTR tetramer and the tetramers of 39 TTR variants tested either clinically or ex vivo.

In Study B3461028 there were 2 genotypes (Pro24Ser and Val20Ile) for whom stabilization was not calculable at any time point during the 30-month study. *Relationship between plasma concentration and effect (new modelling approach for the ATTR-CM application)*

An exposure-response analysis was completed evaluating the % TTR stabilization relative to tafamidis:TTR (TTRR) stoichiometry using all available data. The model was developed using a nonlinear mixed effect modelling approach using the NONMEM software, Version 7.4.1. Factors investigated for their potential impact on model parameters were race (non-Japanese vs. Japanese), patient type (healthy volunteer, ATTR-PN, ATTR-CM), and genotype. For the genotype, the absence or presence (0/1) of effect corresponds to Non-Val30Met vs Val30Met for patients with ATTR-PN, and wild type vs variant for patients with ATTR-CM.

A total of 3662 stabilization observations from 102 healthy volunteers, 152 patients with ATTR-PN (20 Non-Val30Met), and 406 patients with ATTR-CM (340 wild type) were included in the analyses. The relationship between % TTR stabilization and TTRR stoichiometry was adequately described by a sigmoid E_{max} model. The median stoichiometric molar ratio required to provide a half maximal response (EC_{50}) in patients with ATTR-CM was 0.897 (95% CI: 0.741, 1.21) with a maximum response (E_{max}) of 236% (95% CI: 218, 265). A linear time-dependent reduction in maximum stabilization was noted on E_{max} with an average decline of 12.8% per year.

Based on Monte Carlo simulations from the final model, the predicted mean (95% CI) % TTR stabilization in patients with ATTR-CM at 6 months is approximately 147.5% (140.4%, 154.8%) and approximately 205.2% (194.3%, 216.7%) following treatment with tafamidis meglumine 20 mg and 80 mg, respectively. This indicates a greater stabilization with tafamidis meglumine 80 mg compared to 20 mg. Conclusions from this analysis include:

- Relationship between % TTR stabilization and molar ratio of tafamidis:TTR obtained in 11 studies were adequately described by a sigmoid E_{max} model.
- Subject status (healthy volunteers, patients with ATTR-PN and patients with ATTR-CM) were important predictors for both E_{max} and EC_{50}. Healthy volunteers demonstrated the largest maximum stabilization (354%), followed by patients with ATTR-PN (279%) and patients with ATTR-CM (236%). A common EC_{50} (molar ratio of tafamidis to TTR concentration) was estimated for patients with ATTR-CM and ATTR-PN (0.897). The EC_{50} in healthy volunteers was higher (2.23).
- The model indicated that E_{max} decreased over time. However, the mean decay rate was slow (12.8% per year).
- Mean % TTR stabilization is greater in the tafamidis meglumine 80 mg treatment group (205%) compared to the 20 mg group (148%).

An ascending dose study (single oral doses of tafamidis meglumine 240 mg, 350 mg, and 480 mg in healthy subjects) suggested that TTR % stabilization continued to increase beyond the 20mg dose (B3461040).

In the context of the results from the clinical pharmacology Study B3461040 and mean TTR concentrations observed at baseline in patient studies, the 80 mg dose was added to the pivotal phase 3 study in ATTR-CM.

It was assumed for the calculations that: a 20 mg QD tafamidis dose at steady state produces a mean MR in the range of 1.2 to 3.2 from mean minimum concentration at steady state (Cmin,ss) to maximum concentration at steady state (Cmax,ss), which is below the plateau region and that Mean $C_{min,ss}$ to $C_{max,ss}$ following tafamidis doses of 80 mg were expected to produce tafamidis:TTR molar ratios of 3.5 to 9.6, which are approaching or on the plateau region of TTR % stabilization.

2.4.4. Discussion on clinical pharmacology

New dose selection

A new dose of 80mg was selected based on pharmacodynamic studies assessing the relationship between % TTR stabilization and molar ratio (MR) of tafamidis:TTR and clinical studies providing mean TTR concentrations observed in ATTR-CM patients.

Based on the new data, it was assumed for the calculations that: a 20 mg QD tafamidis dose at steady state produces a mean MR in the range of 1.2 to 3.2 from mean minimum concentration at steady state (Cmin,ss) to maximum concentration at steady state (Cmax,ss), which is below the plateau region and that Mean Cmin,ss to Cmax,ss following tafamidis doses of 80 mg were expected to produce tafamidis:TTR molar ratios of 3.5 to 9.6, which are approaching or on the plateau region of TTR % stabilization.

Bioequivalence between 80mg tafamidis meglumine and 61mg free acid tafamidis formulations

***Study B3461054 – bioequivalence study*, single dose:**

This bioequivalence study is considered as most relevant and discriminant, since it has been conducted on single dose, according to the guideline for evaluation of bioequivalence.

However, in this study, demonstration of bioequivalence has not been established.

In fasted state, there was underexposition with 61mg Tafamidis free acid (0.80 fold for C_{max}) compared to 80 mg Tafamidis meglumine.

In fed state there was overexposition with 61mg Tafamidis free acid (1.21 and 1.23 fold for AUClast and Cmax) compared to 80 mg Tafamidis meglumine.

Assessing food effect in Study B3461054 for both treatments,

- for the 61 mg Tafamidis free acid, there was overexposition in fed state (1.32 fold for Cmax),

- for the 80 mg Tafamidis meglumine there was underexposition in fed state (0.85 fold for Cmax)

- AUCs were never impacted by food effect.

Study B3461056 - assessing BE at steady state:

Initially this study was intended mostly to confirm modelings performed.

As single dose comparison (study B3461054) did not meet BE criteria, this multiple dose study was presented by the Applicant to demonstrate BE under steady-state conditions.

At steady state, under fasted condition, bioequivalence could be proven between 61 mg Tafamidis free acid and 80 mg Tafamidis meglumine.

Of note, scientific advice given to the applicant included points relevant for bioequivalence. In particular, regarding how to consider the study of BE at steady state, it was stated that if the BE at single dose failed, "Such an outcome may not necessarily preclude product approval". However, this will be a matter of thorough assessment of all data (including all other comparative pharmacokinetic results) as they are finally considered as a whole." It was also stated that if BE could not be proven, it should be analyzed whether potential differences at steady state in AUC, Cmax and Cmin between the 61 mgA and the 80 mg tafamidis meglumine dose, could be relevant for TTR% stabilisation.

The applicant justified why steady state conditions are the most relevant here. They acknowledged that bioequivalence has not been proven, but in the context, changes in exposure, and higher Cmax in particular, are not expected to be relevant.

2.4.5. Conclusions on clinical pharmacology

Selection of a new high dose of 80mg tafamidis meglumine to conduct the phase 3 study:

The dose of 80mg has been selected based on PK/PD assessment with the objective to reach the maximal TTR % stabilization with adequate safety margin. The final assessment of the results of the phase 3 study, based on efficacy, safety and tolerability data, permitted to conclude on the dose recommended in the SmPC.

New 61mg tafamidis free acid formulation to replace the assessed 4x20mg tafamidis meglumine posology:

As already raised, the bioequivalence could not be formally demonstrated, considering that the multiple dose study is not in line with the Guideline requirements and BE has not been proven after single dose (Cmax values being outside the range 80-125%).

Consequently, it is essential to keep in mind that, on one hand, the formal bioequivalence between both dosages (80mg vs. 61 mg) has not been provided. On the other hand, no clinical efficacy/safety data is available with the 61mg formulation in the sense that the 61mg formulation has not been administered in the randomised blinded clinical pivotal trial. The only expected clinical data for the 61mg formulation will be safety data from the open extension study or observational data.

Thus, the CHMP requested that applicant discuss the clinical relevance of the difference in Cmax, considering that the upper bound of Cmax Confidence Interval at fed state was higher than 125%, and consequently the exposure of the 61mg dose is potentially higher than the expected 80mg exposure. The applicant justified why steady state conditions are the most relevant here. They acknowledged that bioequivalence has not been proven, but in the context, changes in exposure, and higher Cmax in particular, are not expected to be relevant.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response study was conducted with tafamidis in ATTR-CM patients.

The 20mg dose has already been approved for the treatment of ATTR-PN patients and has also been used in the phase 2 study B3461025 conducted in 35 patients with ATTR-CM to evaluate the effects of tafamidis on TTR stabilisation in patients with ATTR-CM due to either variant or wild-type TTR and whether TTR stabilisation can modify cardiac outcomes.

The selection of an additional dose of 80mg for the main study B3461028 was based on PK/PD simulations in order to reach the plateau for maximum TTR stabilisation.

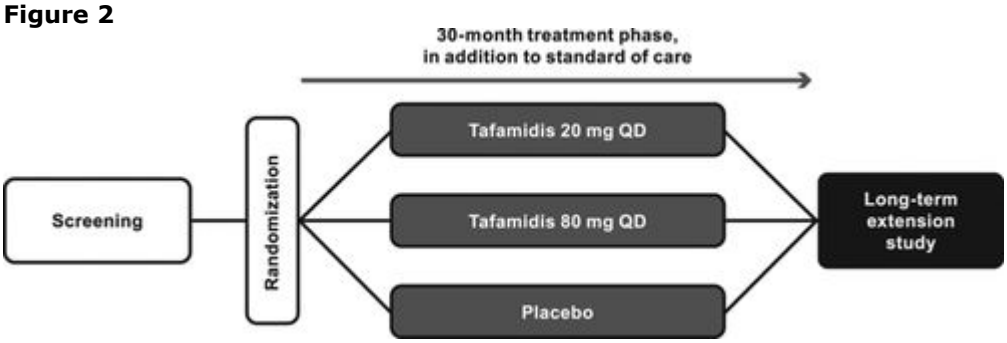
2.5.2. Main study

Study B3461028

Methods

Study B3461028 was a Phase 3, multicentre, international, 3-arm, parallel design, placebo-controlled, randomised study with a 30 month double-blind treatment phase, to determine the efficacy, safety, and tolerability of tafamidis in ATTR-CM patients with either variant or wild-type TTR.

Figure 2



Study Participants

The inclusion criteria were chosen to select patients with:

- ≥18 to ≤90 years of age,
- a history of heart failure evidenced by at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) requiring diuretics,
- a predominant cardiac phenotype; specifically, documented TTR-CM with either wild-type transthyretin or a variant transthyretin genotype (assessed by genotyping),
- evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm.
- the presence of transthyretin amyloid deposits in biopsy tissue (amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain),
- Transthyretin precursor protein identification by immunohistochemistry or mass spectrometry,
- Nuclear scintigraphy using 99mTechnetium-labeled pyrophosphate, hydroxymethylene diphosphonate, or 2-propanodicarboxylic acid is used as a confirmatory test of transthyretin involvement,

- a 6-minute walk test of >100 m; so patients with advanced stage disease (NYHA functional class IV), unlikely to benefit, were not enrolled. Patients with variant TTR-CM, potentially more likely to have a mixed neurologic/cardiac phenotype, may also be more likely to experience difficulties completing this test,

- a plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration ≥600 pg/mL; to ensure patients included in the study have a cardiac cause for their symptoms and to ensure a sufficient event rate within the 30-month duration of the study.

Major exclusion criteria include a confirmed diagnosis of light-chain amyloidosis, previous treatment with tafamidis, an estimated glomerular filtration rate of <25 mL/min/1.73 m^2, and concurrent treatment with nonsteroidal anti-inflammatory drugs, tauroursodeoxycholate and doxycycline, diflunisal, calcium channel blockers, or digitalis. Additional exclusion criteria include modified body mass index of <600 kg/m^2·g/L and heart failure not because of TTR-CM.

Treatments

This study administered tafamidis at 20 mg and 80 mg doses (1× 20 mg capsule of tafamidis meglumine plus 3 × placebo capsules or 4 × 20 mg capsules of tafamidis meglumine) compared with a matched placebo (4 × placebo capsules).

Patients were treated for up to 30 months. Vital status at month 30 was obtained for all patients, including those who discontinued from the study, resulting in mortality data for all patients. Upon completion of the study at the Month 30 visit, patients were eligible for treatment with tafamidis in a separate extension study (B3461045).

Objectives

The primary objective of this study was to assess the efficacy of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules based on all-cause mortality and on frequency of cardiovascular-related hospitalizations, as well as to assess safety and tolerability in comparison to placebo.

Outcomes/endpoints

The primary analysis used in this study was the method of Finkelstein-Schoenfeld applied to the hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations (defined as the number of times a patient is hospitalised [ie, admitted to a hospital] for CV-related morbidity) during the trial, comparing the pooled tafamidis patient group (20 mg and 80 mg dose groups combined) to placebo.

Key secondary endpoints were change from Baseline to Month 30 in the 6MWT and the KCCQ-OS score and were controlled for multiplicity.

A 6MWT was conducted during the Screening period and at the Baseline visit and at Month 6, 12, 18, 24, and 30 visits (or Early Study Discontinuation). 6MWT correlates with quality of life, NYHA class, peak exercise capacity, and hospitalisation and mortality rates in patients with CHF. 6MWT is considered an appropriate measurement of response to medical intervention in patients with moderate to severe CHF;

Patients completed the KCCQ at the Baseline visit and at Months 6, 12, 18, 24, and 30 (or Early Study Discontinuation). The KCCQ is a 23-item patient completed questionnaire that assessed health status

and health related quality of life in patients with heart failure. Items assess the ability to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and health related quality of life. Scoring yields scores for 8 domains (Physical limitation, Symptom stability, Symptom frequency, Symptom Burden, Total Symptom, Self-efficacy, Social limitation, and Quality of life) as well as a Clinical Summary score and an Overall Summary score. Domain scores are transformed to a 0 to 100 range; higher scores indicate better health status.

The remaining secondary and exploratory analyses/endpoints were not adjusted for multiplicity. Secondary endpoints included CV-related mortality, frequency of CV-related hospitalisation, all-cause mortality, and TTR stabilisation at Month 1.

Randomisation and blinding

There were 441 patients enrolled into the study, randomised 2:1:2 to the 3 arms of the study in the following manner: n=177 in the placebo arm, n=88 in the tafamidis meglumine 20 mg arm, and n=176 in the tafamidis meglumine 80 mg arm.

Patients were stratified by TTR genotype (variant and wild-type), Baseline NYHA classification (NYHA Class I and NYHA Classes II and III combined) and region (US and ex-US). Enrolment of wild-type patients was stopped to allow enrolment of more patients with variant type, with the goal of enrolment of at least 30% of each variant and wild-type.

Statistical methods

The primary analysis applied the method of Finkelstein-Schoenfeld to the hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations during the study, combining the patients in the tafamidis 20 mg and tafamidis 80 mg groups (including patients in 80 mg group that may have had a dose reduction to 40 mg) into 1 pooled group. This pooled group (tafamidis) was compared with the placebo group as the prespecified primary comparison of interest. To maintain the experiment-wise type 1 error rate at or below the specified level of 0.05, a pre-specified hierarchical order for testing the primary and key secondary endpoints was used. The multiplicity procedure was applied to the ITT analysis set only.

The Finkelstein-Schoenfeld test, a generalisation of the Wilcoxon rank-sum test, is based on the principle that each patient in the study is compared to every other patient within each stratum in a pair wise manner. The method recognises the higher importance of all-cause mortality. The pair wise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning a +1 to the "better" patient and a -1 to the "worse" patient. If both patients are dead, then the patient with a longer survival time is assigned +1 and the one with the shorter survival time a -1. If 1 patient is alive and the other is not, the live patient receives a +1 and the deceased one a -1. If both patients are alive, the comparison uses CV-related hospitalisation to assign scores. The patient with the fewer CV- related hospitalisation (frequency) receives a +1 while the other receives -1. A score, u_{ij}, represents the pair-wise comparison and indicates whether patient i has the more favourable outcome than patient j. The test statistic is based on the sum of these scores. The "cardiovascular-related hospitalisation" in all analyses, unless otherwise specified, combines hospitalisations adjudicated as CV-related with hospitalisations adjudicated as indeterminate.

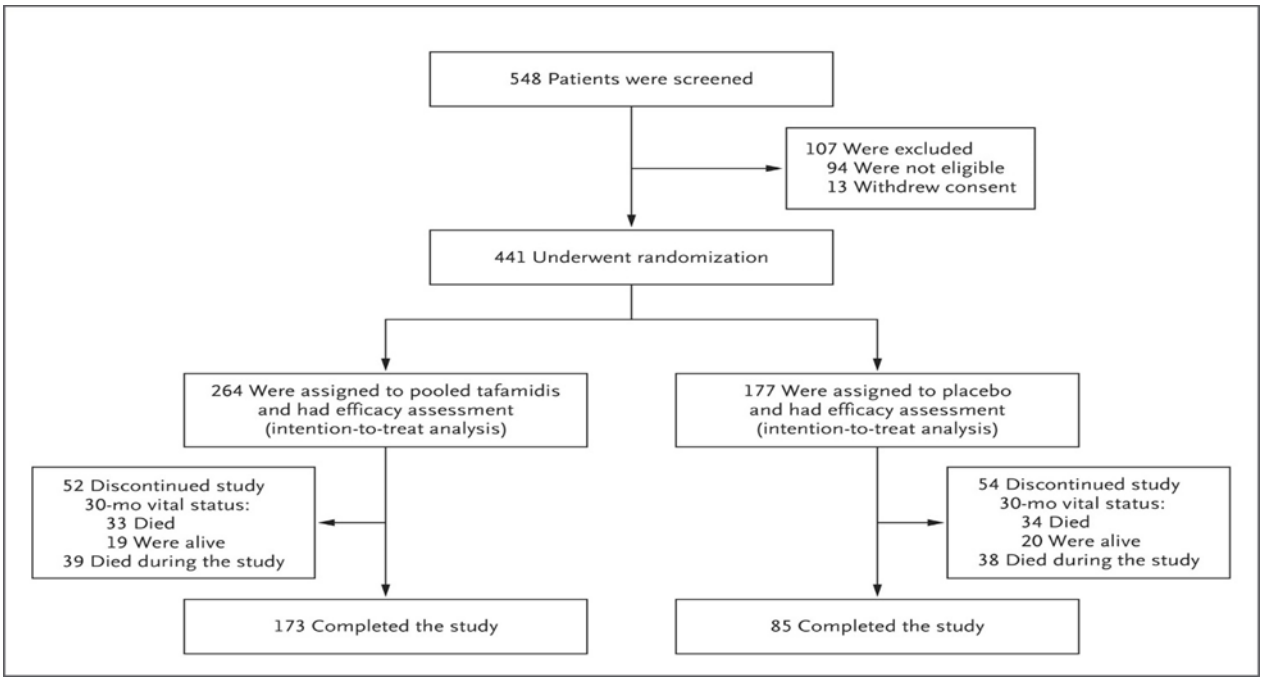
Patients who discontinued for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the primary analysis and all analyses involving survival (except select sensitivity analyses) in the same manner as death.

Exploratory sensitivity analyses with multiple imputation were also performed to account for missing hospitalisation data. Dropouts were the only source of missing hospitalisation data. A total of 258 patients completed the study.

Results

Participant flow

Figure 3



Recruitment

From December 2013 through August 2015, a total of 548 patients were screened and 441 patients enrolled at 48 sites in 13 countries; 264 patients received tafamidis (80 mg or 20 mg) and 177 patients received placebo.

Conduct of the study

Baseline data

Table 1: Demographic and Baseline Characteristics (ITT Population) – Study B3461028

	Tafamidis Meglumine 20 mg (N=88)	Tafamidis Meglumine 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
Age (years)[1]				
n	88	176	264	177
Mean (SD)	73.3 (7.07)	75.2 (7.24)	74.5 (7.23)	74.1 (6.69)
Min, Max	51, 86	46, 88	46, 88	51, 89
Sex - n(%)				

Table 1: Demographic and Baseline Characteristics (ITT Population) – Study B3461028

	Tafamidis Meglumine 20 mg (N=88)	Tafamidis Meglumine 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
Male	83 (94.3)	158 (89.8)	241 (91.3)	157 (88.7)
Female	5 (5.7)	18 (10.2)	23 (8.7)	20 (11.3)
Race - n (%)				
White	75 (85.2)	136 (77.3)	211 (79.9)	146 (82.5)
Black	11 (12.5)	26 (14.8)	37 (14.0)	26 (14.7)
Asian	2 (2.3)	11 (6.3)	13 (4.9)	5 (2.8)
Other	0	3 (1.7)	3 (1.1)	0
NYHA Baseline Classification- n (%) [2]				
NYHA Class I	8 (9.1)	16 (9.1)	24 (9.1)	13 (7.3)
NYHA Class II	57 (64.8)	105 (59.7)	162 (61.4)	101 (57.1)
NYHA Class III	23 (26.1)	55 (31.3)	78 (29.5)	63 (35.6)
Baseline Stratification- n (%) [2]				
NYHA Class I and II	65 (73.9)	121 (68.8)	186 (70.5)	114 (64.4)
NYHA Class III	23 (26.1)	55 (31.3)	78 (29.5)	63 (35.6)
Wild-type TTR Genotype	67 (76.1)	134 (76.1)	201 (76.1)	134 (75.7)
Variant TTR Genotype	21 (23.9)	42 (23.9)	63 (23.9)	43 (24.3)
Variant TTR Genotype/NYHA Class I and II	12 (13.6)	22 (12.5)	34 (12.9)	24 (13.6)
Variant TTR Genotype/NYHA Class III	9 (10.2)	20 (11.4)	29 (11.0)	19 (10.7)
Wild-type TTR Genotype/NYHA Class I and II	53 (60.2)	99 (56.3)	152 (57.6)	90 (50.8)
Wild-type TTR Genotype/NYHA Class III	14 (15.9)	35 (19.9)	49 (18.6)	44 (24.9)
US	63 (71.6)	108 (61.4)	171 (64.8)	108 (61.0)
Non-US	25 (28.4)	68 (38.6)	93 (35.2)	69 (39.0)
Duration since TTR-CM diagnosis (years)				
Mean (SD)	1.206	0.932	1.023	1.233
SD	1.5711	1.1789	1.3259	1.4388
Median	0.559	0.561	0.559	0.671
Min, Max	0.003, 9.958	0.003, 6.888	0.003, 9.958	0.003, 7.888

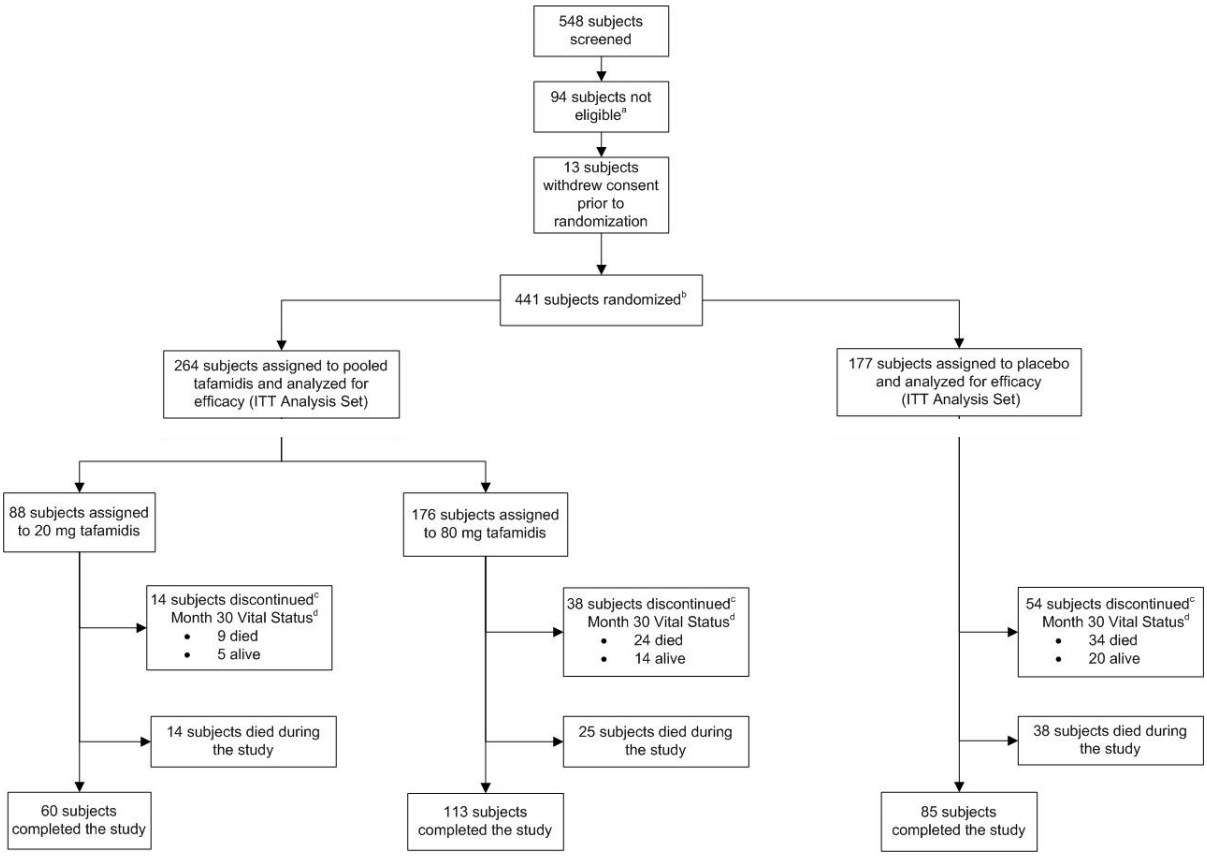
Source: S0115 Module 5.3.5.1 B3461028 Report Body Table 14.1.2.1.1.1; Table 14.1.2.1.1.1.1

[1] Age at screening. Age is calculated as screening date year – birth year. If the screening date month is less than the DOB month, or the screening date month = DOB month and the screening date day is less than the DOB day, then age = (screening date year - DOB year) –1.

[2] NYHA class: I = without resulting limitations, II = slight limitation, III = marked limitation, IV = inability to carry on any physical activity without discomfort.

Numbers analysed

Figure 4: Subject Disposition



Note: Numbers do not depict death count for purpose of primary analysis. Some reasons for discontinuation (ie, transplants involving the heart and implantation of a CMAD) were treated as death in the primary analysis a. The most common reasons for screen failure include: enrollment closure for wild-type subjects; NT-proBNP <600; clinically unstable and eGFR <25 mL/min/1.73 m2.
b. Subjects were randomized to placebo, tafamidis 20 mg, and tafamidis 80 mg in a 2:1:2 ratio.
c. Discontinuation reasons: Tafamidis 20 mg – 8 no longer willing to participate; 5 due to AE; 1 organ transplant. Tafamidis 80 mg – 17 no longer willing to participate; 12 due to AE; 5 organ transplant; 2 CMAD implant; 1 Lost to follow up; 1 protocol violation. Placebo – 37 no longer willing to participate; 11 due to AE; 5 organ transplant; 1 protocol violation.
d. Month 30 vital status obtains alive/dead status from time of discontinuation through the Month 30 time point.
Abbreviations: AE = adverse event; CMAD = cardiac mechanical assist device implantation; eGFR = estimated glomerular filtration rate; ITT = Intent to Treat analysis set; NT-proBNP = N-terminal pro b-type natriuretic peptide

Table 2: Subject Disposition

Number (%) of Subjects	Tafamidis 20 mg n (%)	Tafamidis 80 mg n (%)	Pooled Tafamidis n (%)	Placebo n (%)	Total[a] n (%)
Assigned to study treatments	88	176	264	177	441
Treated	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Completed[b]	60 (68.2)	113 (64.2)	173 (65.5)	85 (48.0)	258 (58.5)
Discontinued[c]	14 (15.9)	38 (21.6)	52 (19.7)	54 (30.5)	106 (24.0)
Death	14 (15.9)	25 (14.2)	39 (14.8)	38 (21.5)	77 (17.5)
Analyzed for Efficacy					
ITT Analysis set	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Per-Protocol Analysis set	84 (95.5)	171 (97.2)	255 (96.6)	169 (95.5)	424 (96.1)
Analyzed for Safety[d]	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)
Adverse events[e]	87 (98.9)	175 (99.4)	262 (99.2)	175 (98.9)	437 (99.1)
Laboratory data[f]	88 (100.0)	176 (100.0)	264 (100.0)	177 (100.0)	441 (100.0)

Source: Table 14.1.1.1 and Table 14.1.1.1.1
a. Total = pooled tafamidis + placebo.
b. The number of subjects completed is derived from the subject summary electronic case report form.
c. Discontinued from study other than death.

d. Analyzed for safety tabulates the number of subjects treated.
e. Adverse events tabulates the number of subjects who have reported an AE.
f. Laboratory data tabulates the number of subjects who have at least 1 lab result.

Outcomes and estimation

According to the primary analysis performed with the Finkelstein-Schoenfeld method, treatment with tafamidis was superior to placebo over 30 months (p<0.001). Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisations for the pooled active treatment is provided in Table 3 below.

Table 3: Primary Analysis - Finkelstein-Schoenfeld Analysis of All-Cause Mortality and Frequency of Cardiovascular-related Hospitalisations (ITT Population) – Study B3461028

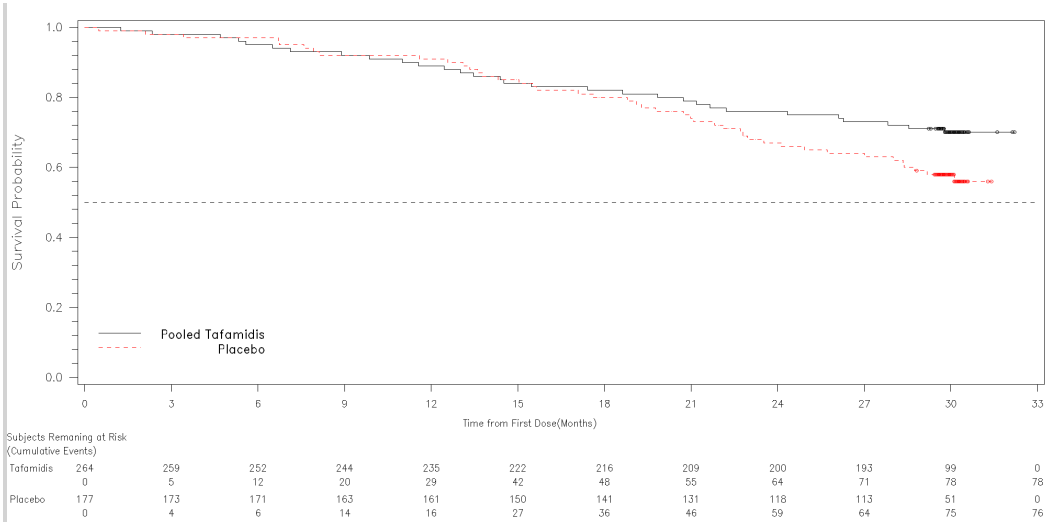
	Pooled Tafamidis (N=264)	Placebo (N=177)
Number (%) of Patients Alive at Month 30	186 (70.5)	101 (57.1)
Average frequency of CV Hospitalisations during 30 months (per patient per year) among those alive at Month 30 [1]	0.297	0.455
p-value from Finkelstein-Schoenfeld method [2]	0.0006	

Source: S0115 Module 5.3.5.1 B3461028 Report Body Table 14.2.1.1; Table 14.2.2.1.1.
Note: Heart transplants and cardiac mechanical assist device implantation were treated as death.
[1] CV-related hospitalisations per year is calculated as (Patients' number of CV-related hospitalisations) / (duration on study in years).
[2] The Finkelstein-Schoenfeld test is a hierarchical comparison of mortality and cardiovascular-hospitalisation. Within each stratum, each patient in the clinical study is compared with every other patient within each stratum in a pairwise manner.
The primary analysis tests if the hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations is different between the tafamidis and placebo treatment groups.
Only CV-related hospitalisations where the patient is admitted to a hospital during the trial are included in this analysis; any hospitalisations prior to randomisation date are not included.

The win ratio method (number of pairs of the treated patient wins divided by number of pairs of placebo patient wins) may be helpful in interpreting the Finkelstein-Schoenfeld result. In a post hoc analysis, the win ratio for the primary analysis is 1.695 (95% CI 1.255, 2.289), indicating that a tafamidis-treated patient had a 69.5% higher chance of having a better outcome based on a hierarchical combination of all-cause mortality and CV-related hospitalisation relative to a placebo patient.

A Kaplan-Meier plot of all-cause mortality with heart transplants and cardiac mechanical assist devices handled in the same manner as death is presented in Figure 5. Overall, all-cause mortality for the pooled tafamidis and placebo groups was 78 patients (29.5%) and 76 patients (42.9%), respectively. There were 186 patients (70.5%) and 101 patients (57.1%) in the pooled tafamidis and placebo groups, respectively, censored because they were alive at the time of analysis. The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259).

Figure 5: Kaplan-Meier Plot of All-cause Mortality (ITT Population) – Study B3461028



Source: S0115 Module 5.3.5.1 B3461028 Report Body Figure 14.2.5.3.1
Note: o Indicates censored observations

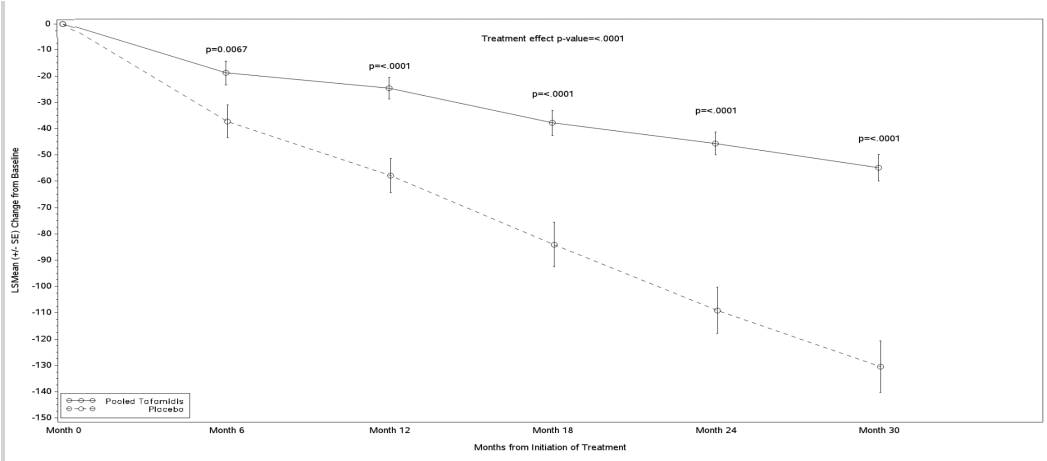
Regarding the frequency of CV-related hospitalisations for the pooled active treatment, there were 138 (52.3%) and 107 (60.5%) patients with at least 1 CV-related hospitalisation in the pooled tafamidis and placebo groups, respectively. The frequency of CV-related hospitalisation per year was 0.4750 (95% CI 0.4181, 0.5396) and 0.7025 (95% CI 0.6174, 0.7993) for the pooled tafamidis and placebo groups, respectively. The treatment difference (hereafter referred to as relative risk ratio) between the pooled tafamidis and placebo groups was 0.6761, indicating a significant reduction in the risk of CV-related hospitalisation in the tafamidis group relative to placebo (p <0.0001).

6MWT - Change from Baseline to Month 30 in Distance Walked

There was a statistically significant and clinically meaningful difference favouring the tafamidis-treated group versus the placebo group in the change from Baseline to Month 30 in the distance walked during the 6-Minute Walk Test (6MWT).

At Baseline, mean (standard deviation [SD]) 6MWT distance in metres were similar for the pooled tafamidis (350.55 [121.296]) and placebo groups (353.26 [125.983]). At Month 30, the LS mean (standard error [SE]) change from Baseline for the pooled tafamidis and placebo groups was -54.87 (5.068) metres and -130.55 (9.798) metres, respectively. The pooled tafamidis least squares (LS) mean (standard error [SE]) change from baseline difference from placebo was 75.68 (9.236) metres (p<0.0001). A statistically significant treatment effect favouring tafamidis was first observed at Month 6 (p=0.0067) and remained significant through Month 30 (Figure 6).

Figure 6: Distance Walked During 6MWT LS Means (SE) (ITT Population) – Study B3461028



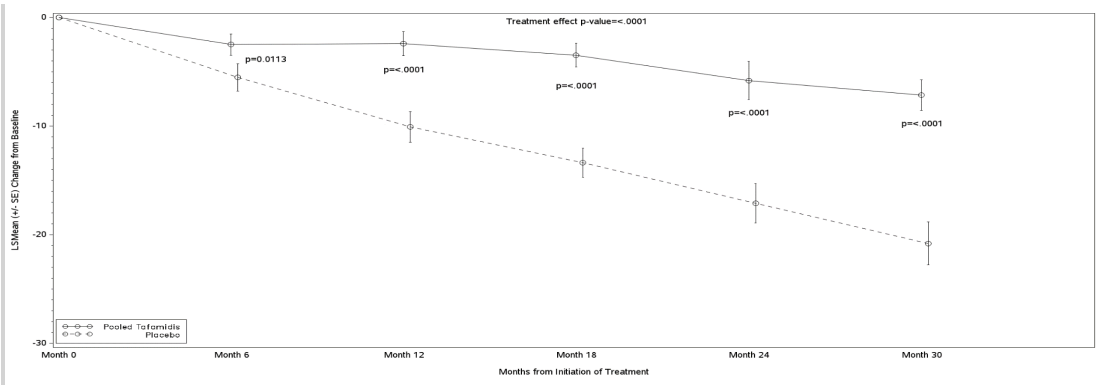
Source: S0115 Module 5.3.5.1 B3461028 Report Body Figure 14.2.3.1.1
Abbreviations: 6MWT=6-Minute Walk Test; ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; MMRM = Mixed Model Repeated Measure; SE=standard error
LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type) , and visit by treatment interaction, as fixed effects and baseline score as covariate.

KCCQ-OS - Change from Baseline to Month 30 in KCCQ-OS Score

There was a statistically significant and clinically meaningful difference in quality of life favouring the tafamidis-treated group versus the placebo group as measured by the change from Baseline to Month 30 on the KCCQ-OS score.

At Baseline, mean (SD) KCCQ-OS scores were similar for the pooled tafamidis (67.274 [21.3561]) and placebo groups (65.898 [21.7357]). At Month 30, the LS mean (SE) change from Baseline for the pooled tafamidis and placebo groups was -7.16 (1.415) and -20.81 (1.971), respectively. The pooled tafamidis LS mean (SE) difference from placebo was 13.65 (2.130) points (p<0.0001). A significant treatment effect favouring tafamidis was first observed at Month 6 (p=0.0113) and remained consistent through Month 30 (Figure 7).

Figure 7: KCCQ-OS Score LS Means (SE) Change From Baseline to Month 30 (ITT Population) – Study B3461028

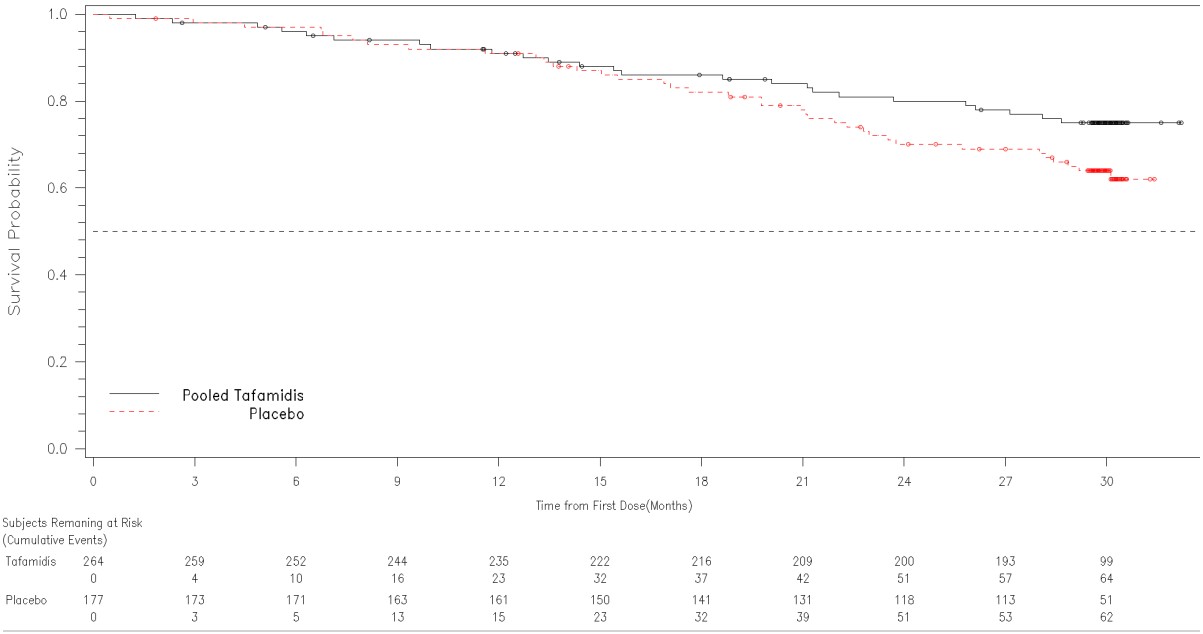


Source: S0115 Module 5.3.5.1 B3461028 Report Body Figure 14.2.4.1.1
Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS=least squares; MMRM = Mixed Model Repeated Measure; SE=standard error
Notes: KCCQ-OS score is calculated as the mean of Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation Scores. LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type) , and visit by treatment interaction , as fixed effects and baseline score as covariate.

CV-related Mortality – Secondary Endpoint

Tafamidis-treated patients had a significantly reduced CV-related mortality relative to placebo-treated patients. The hazard ratio from the CV-related mortality Cox-proportional hazard model was 0.691 (95% CI 0.488, 0.980), indicating a 30.9% reduction in the risk of death in the pooled tafamidis group relative to the placebo group (p=0.0383). Heart transplantation and combined heart and other organ transplantation, or the implantation of a cardiac mechanical assist device, were handled in the same manner as death.

Figure 8: Kaplan-Meier Plot of Cardiovascular-related Mortality (ITT Population) – Study B3461028



Subjects Remaining at Risk (Cumulative Events)

Tafamidis	264 0	259 4	252 10	244 16	235 23	222 32	216 37	209 42	200 51	193 57	99 64
Placebo	177 0	173 3	171 5	163 13	161 15	150 23	141 32	131 39	118 51	113 53	51 62

Source: S0115 Module 5.3.5.1 B3461028 Report Body Figure 14.2.5.1.1.
Note: o Indicates censored observations

When heart transplants and cardiac mechanical assist devices were not assumed as death, the hazard ratio from the cardiovascular-related mortality Cox-proportional hazard model was 0.663 (95% CI 0.461, 0.954), indicating a 33.7% reduction in the risk of death in the pooled tafamidis group relative to the placebo group (p=0.0267).

TTR Stabilisation at Month 1 – Secondary Endpoint

At Month 1 (pre-dose sample), significantly more patients in the pooled tafamidis group (211 patients, 86.1%) demonstrated TTR stabilisation than was observed for patients in the placebo group (6 patients, 3.5%), (p<0.0001). Similar results were obtained from the sample collected which targeted the time of maximum concentration (Month 1, 4 hours 30 minutes).

In study B3461028, there were 2 genotypes (Pro24Ser and Val20Ile) in 3 patients for whom stabilisation was not calculable at any post-baseline time point. All 3 patients were NYHA Class II at Baseline and randomised to the tafamidis meglumine 80 mg arm.

Ancillary analyses

Subgroup Analyses

Study B3461028 was not powered to evaluate response by subgroups such as tafamidis dose, TTR genotype, or Baseline NYHA classification. However, pre-specified exploratory analyses were conducted to understand the effect of the 2 doses administered, as well to explore efficacy within the subgroups.

Subgroup Analyses of the primary analysis endpoint, its individual components (all-cause mortality and frequency of CV-related hospitalisation) and secondary endpoint CV-related mortality

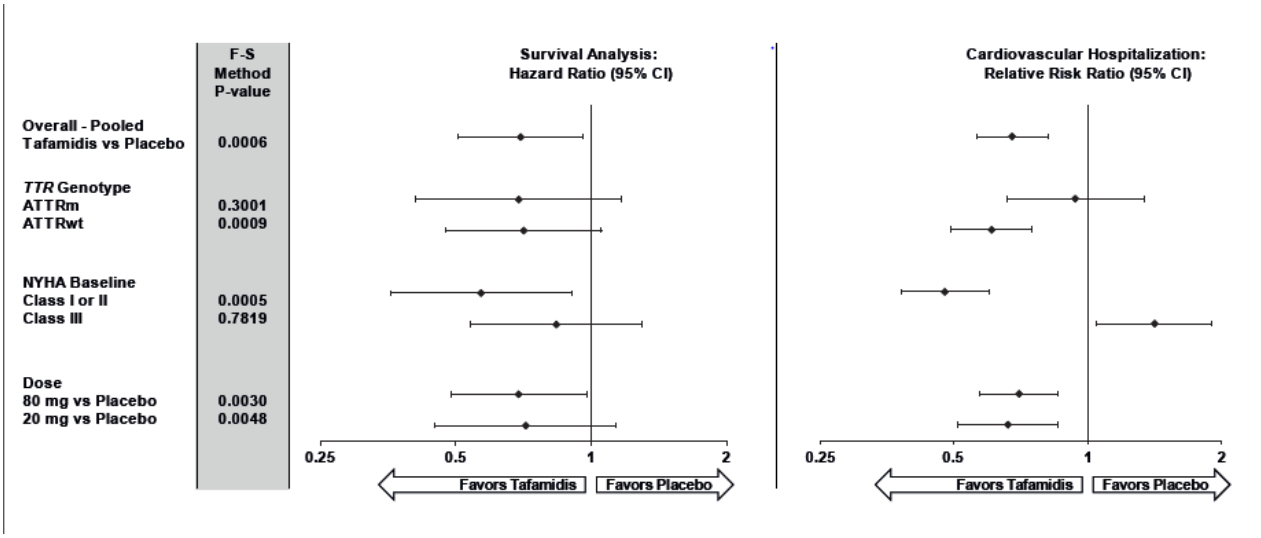
A forest plot of treatment effects by dose, TTR genotype, and Baseline NYHA classification (Figure 9) illustrates the treatment effect favouring tafamidis over placebo for all-cause mortality in all subgroups, and for CV-related hospitalisations in all subgroups except NYHA Class III.

Key findings included:

- A significant treatment effect favouring both the 20 mg and 80 mg tafamidis doses compared with placebo (p=0.0048 and 0.0030, respectively). The clinical efficacy of tafamidis in the overall ATTR-CM population was comparable across the 20 and 80 mg dose groups.
- A significant treatment effect favouring tafamidis compared to placebo was observed in patients with the wild-type TTR genotype (n=335, p=0.0009). The treatment effect observed between pooled tafamidis and placebo patients with the variant TTR genotype was directionally consistent with the data in wild-type patients (n=106, p=0.3001).

  A significant treatment effect favouring tafamidis was found for patients with NYHA Class I and II combined baseline classification (p=0.0005). However, a significant treatment effect for tafamidis was not observed for patients with baseline NYHA Class III classification (p=0.7819). Though the treatment effect was not statistically significant, the mortality benefit was directionally consistent and favourable with tafamidis (Figure 9). However, the significantly higher hospitalisation rate observed in the tafamidis-treated NYHA III subgroup compared to placebo may be attributable to longer survival with an advanced phenotype which may be associated with more frequent hospitalisations.

Figure 9: All-Cause Mortality Hazard Ratio and Frequency of Cardiovascular Related Hospitalisation Relative Risk Ratio by Subgroup (ITT Analysis Data Set)



Source: S0115 Module 5.3.5.1 B3461028 Report Body Table 14.2.1.1; Table 14.2.1.2; Table 14.2.1.7; Table 14.2.1.9; Table 14.2.2.1; Table 14.2.2.2; Table 14.2.2.6; Table 14.2.2.8; Table 14.2.5.3.1; Table 14.2.5.3.3; Table 14.2.5.3.4; Table 14.2.5.3.5..

Treatment effects favouring tafamidis over placebo in CV-related mortality were also observed across both tafamidis doses, in patients with both variant and wild-type TTR genotype, and for NYHA Class I and Class II patients.

Subgroup analyses for the key secondary endpoints (6MWT distance and KCCQ-OS score at Month 30)

6 MWT distance - This benefit is further reflected in the subgroup analyses where results by tafamidis dose, genotype, and baseline NYHA classification demonstrated a significant treatment effect favouring tafamidis vs placebo in the change from Baseline to Month 30 in the distance walked during the 6MWT. A significant treatment effect favouring both the tafamidis 20 mg and tafamidis 80 mg doses versus placebo was first observed at Month 6 (p=0.0339 and p=0.0240, respectively) and remained consistent through Month 30. The treatment effect was comparable between the doses of 20 mg and 80 mg. Significant treatment effects favouring tafamidis were first observed at Month 24 (p=0.0172) for patients with variant TTR and at Month 6 (p=0.0170) for patients with wild-type TTR. Both treatment effects remained consistent through Month 30. Significant treatment effects favouring tafamidis were first observed at Month 6 (p=0.0013) for NYHA Class I and II combined, which remained significant through Month 30. A significant treatment effect was observed only at Month 24 (p=0.0096) for patients with NYHA Class III baseline classification.

KCCQ-OS - Analysis by subgroups (tafamidis dose, TTR genotype, and baseline NYHA classification) demonstrated treatment effects favouring tafamidis over placebo across subgroups. A significant treatment effect favouring the 80 mg tafamidis dose was first observed at Month 6 (p=0.0273), and for the tafamidis 20 mg dose a significant treatment effect favouring tafamidis was first observed at Month 12 (p=0.0005). Both remained significant through Month 30. The treatment effect was comparable between the doses of 20 mg and 80 mg. Significant treatment effects favouring tafamidis were first observed at Month 12 (p=0.0034) for patients with variant TTR and at Month 6 (p=0.0412) for patients with wild-type TTR. A significant treatment effect favouring tafamidis in NYHA Class I and II combined baseline classification was first observed at Month 6 (p=0.0100) and remained significant through Month 30. Significant treatment effects were observed for patients with NYHA Class III baseline classification at Months 18 and 30 (p=0.0264 and p=0.0090, respectively).

TTR Stabilisation – Exploratory Endpoint

At Month 1, a significantly greater proportion of subjects in the tafamidis 20 mg group (67/81 [82.7%] subjects) and tafamidis 80 mg group (144/164 [87.8%] subjects) demonstrated TTR stabilization than was observed for subjects in the placebo group (6/170 [3.5%] subjects) (p <0.0001). Similar results were obtained from the sample collected which targeted the time of maximum concentration (Month 1 - 4 hours 30 minutes).

At Month 1, a significantly greater proportion of subjects in the tafamidis group with variant (33/56 [58.9%] subjects) or wild-type (178/189 [94.2%] subjects) demonstrated TTR stabilization than was observed for subjects in the placebo group (0/39 [0%] and 6/131 [4.6%] subjects, respectively) (p <0.0001).

NT-proBNP and Troponin I – Exploratory Endpoints

Change from Baseline in NT-proBNP concentration in the pooled tafamidis group was an exploratory endpoint in Study B3461028. NT-proBNP has prognostic value for ATTR-CM patients with heart failure or left ventricular dysfunction and was shown to be a significant predictor for mortality in an exposure-efficacy longitudinal analysis.

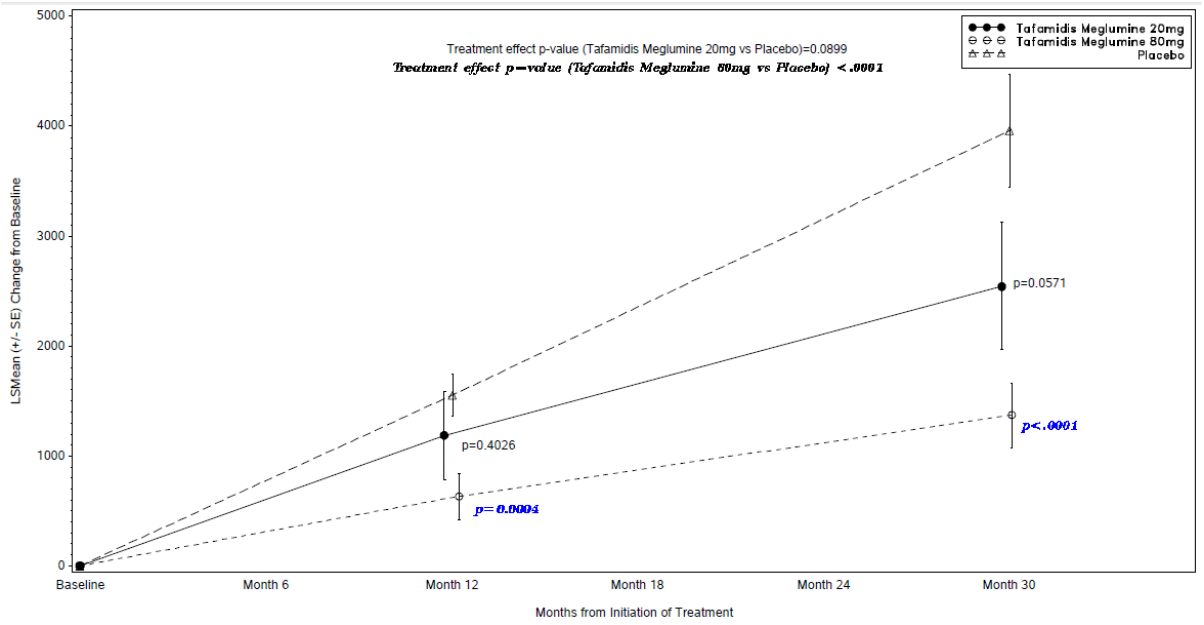
The LS mean (SE) Month 30 change from Baseline difference in NT-proBNP concentration from the placebo group was -2180.54 (583.218) (p=0.0002) for the pooled tafamidis group. Post-hoc analyses of change from Baseline in NT-proBNP concentration by dose at Month 12 and Month 30 were also conducted.

Table 4: Change From Baseline at Month 12 and Month 30 in NT-proBNP Concentration – By Dose (ITT Population) – Study B3461028

N-terminal pro-Brain Natriuretic Peptide (PG/ML) Visit	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Placebo (N=177)
Baseline			
n	88	176	177
Mean (SD)	3963.842 (3904.6022)	3941.093 (3090.0137)	3845.503 (2971.5497)
Median	2681.957	3122.009	3161.026
Month 12 – Change from Baseline			
n	72	142	140
Median	440.679	-4.237	701.502
LS Mean (SE)	1185.82 (400.824)	633.22 (207.613)	1553.65 (189.492)
LS Mean (SE) Difference From Placebo	-367.84 (439.169)	-920.43 (257.459)	
Difference p-value	0.4026	0.0004	
Month 30 – Change from Baseline			
n	60	110	80
Median	863.502	95.500	2561.634
LS Mean (SE)	2542.23 (577.783)	1371.71 (296.336)	3959.25 (511.014)
LS Mean (SE) Difference From Placebo	-1417.02 (743.378)	-2587.54 (570.248)	
Difference p-value	0.0571	<0.0001	
LS Mean (SE) 20 mg vs 80 mg		1170.51 (587.31)	
95% CI of Difference		16.87, 2324.16	
Difference p-value		0.0468	

Source: Module 5.3.5.3 SCE Table 14.2.6.14.1.1.1
Abbreviations: ANCOVA = analysis of covariance; ITT = Intent-to-treat; LS = least squares; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; MMRM = Mixed Model Repeated Measure; SD = Standard Deviation; SE = Standard Error; TTR = transthyretin
LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix (or as appropriate); center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild type), and visit by treatment interaction, as fixed effects and Baseline score as covariate

Figure 10: NT-proBNP Concentration LS Means (SE) Change from Baseline to Month 30 By ose (ITT Population) – Study B3461028



Source: Module 5.3.5.3 SCE Figure 14.2.6.14.1.1.2
Abbreviations: ANCOVA = analysis of covariance; ITT = Intent-to-Treat; LS = least squares; MMRM = Mixed Model Repeated Measure; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; SE = standard error; TTR = transthyretin.
Note: LS means are from an ANCOVA (MMRM) model with an unstructured covariance matrix (or as appropriate); center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild type), and visit by treatment interaction, as fixed effects and baseline score as covariate.
P-values in blue refer to Tafamidis Meglumine 80 mg versus Placebo

A post-hoc analysis of change from Baseline at Month 12 and Month 30 in troponin I concentration was conducted. The tafamidis meglumine 20 mg group had an LS mean difference in change from Baseline to Month 30 from placebo of -0.06 ng/mL, while the tafamidis meglumine 80 mg group had a larger LS mean difference from placebo of -0.10 ng/mL, directionally favouring the 80 mg dose (p=0.2479).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 5: Summary of efficacy for trial B3461028

Title: Tafamidis - Transthyretin Amyloid Cardiomyopathy (ATTR-CM)			
Study identifier	Study B3461028		
Design	Phase 3, international, 3-arm, parallel design, placebo-controlled study with a 30-month double-blind treatment phase to determine the efficacy, safety, and tolerability of tafamidis in patients with ATTR-CM.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		30 Months <time> <not applicable> 60 Months
Hypothesis	Superiority		
Treatments groups	Arm-1		Tafamidis 20 mg. 30 Months, 88 randomized
	Arm-2		Tafamidis 80 mg. 30 Months, 176 randomized
	Arm-3		Placebo. 30 Months, 177 randomized
Endpoints and definitions	All-cause mortality	Primary Endpoint	In ATTR-CM, elevated NT-proBNP (>3000 pg/mL) has been reported to be significantly associated with increased mortality
	Frequency of CV-related hospitalisations	Primary Endpoint	Troponin I may be predictive of CV-related hospitalization If LS mean difference in change from Baseline to Month 30 in ng/mL is smaller in a group it is considered negative
	Change from baseline to Month 30 in 6MWT (key)	Secondary Endpoint	If a patient can walk longer after months it is considered positive
	Change from baseline to Month 30 in quality of life on the KCCQ-OS score	Secondary Endpoint	The KCCQ-OS score evaluate the increase or decrease of the quality of life during months
Database lock	07 February 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Patients were stratified by TTR genotype (variant and wild-type) and by Baseline NYHA classification (NYHA Class I and NYHA Classes II and III combined) at randomisation. The inclusion criteria were chosen to select patients with a predominant cardiac phenotype; specifically, documented TTR-CM with either wild-type transthyretin or a variant transthyretin genotype, ≥18 to ≤90 years of age, a history of heart failure evidenced, a 6-minute walk test of >100 m and a plasma NT-proBNP concentration ≥600 pg/mL are required. Major exclusion criteria include a confirmed diagnosis of light-chain amyloidosis, previous treatment with tafamidis, an estimated glomerular filtration rate of <25 mL/min/1.73 m^2, and concurrent treatment with nonsteroidal anti-inflammatory drugs, tauroursodeoxycholate and doxycycline, diflunisal, calcium channel blockers, or digitalis. Additional exclusion criteria include modified body mass index of <600 $kg/m^2 \cdot g/L$ and heart failure not because of TTR-CM.			
Descriptive statistics and estimate variability	Treatment group	Tafamidis meglumine 20mg	Tafamidis meglumine 80mg	Placebo
	Number of subject	88	176	177
		264		177
	All-cause mortality	Reduction of 30.2%		±
	HR	0.698		
	95% CI	(0.508, 0.958)		
	p	0.0259		
	Frequency of CV-related hospitalisations	Reduction of 32.4%		±
	RR	0.6761		
	95% CI	(0.5639, 0.8107)		
	p	<0.0001		
	Change from baseline to Month 30 in 6MWT (key)	LS mean 75.68 metres SE 9.236 metres		±
	p	<0.0001		
	Change from baseline to Month 30 in quality of life on the KCCQ-OS score	LS mean 13.65 points SE 2.130 points		±
	p	<0.0001		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive studies

Supportive study B3461025 (Fx1B-201)

Study B3461025 was an open-label, multicentre, single-treatment, 12-month Phase 2 study to evaluate the effects of tafamidis on TTR stabilisation in patients with ATTR-CM due to either variant or wild-type TTR and whether TTR stabilisation can modify cardiac outcomes. Potential treatment effects across a number of clinical outcomes were also assessed. Although there was no comparator group, data from 29 patients with ATTR-CM (11 patients with Val122Ile, 18 patients with wild-type) in Study B3461024 (TRACS), was used as a historical control group. In Study B3461025, 35 enrolled patients were treated with tafamidis 20 mg soft gelatin capsules once daily for 6 weeks, and those who completed 6 weeks continued for up to a total of 12 months. The enrolled patients were elderly, with significant disease duration at the time of enrollment, and significant co-morbidities.

Tafamidis was effective in achieving and maintaining TTR stabilisation in both wild type and Val122Ile patients. TTR stabilisation, as assessed by the immunoturbidimetric assay, was achieved in 97.1% of patients at Week 6. At Months 6 and 12, TTR stabilisation was 88.2% and 87.5%, respectively.

Following 12 months treatment with tafamidis, along with routine standard of care, 2/35 patients (5.7%) died, 9/35 patients (25.7%) experienced at least 1 CV hospitalisation, and 9/35 patients (25.7%) experienced the composite endpoint of death or CV hospitalisation. Results were similar between the TTR genotype groups. These data were numerically better than that reported in the TRACS historical control cohort, during which the 12-month rate of death, CV hospitalisations and death/CV hospitalisations combined were 6/29 (20.7%), 10/29 (34.5%) and 13/29 (44.8%), respectively.

At baseline, the extensive cardiac involvement in all patients was clearly demonstrated by multiple assessments, including echocardiography, cardiac MRI, chest X-ray, cardiac biomarkers, ECG/Holter monitoring, the health-related quality of life questionnaires, and the 6MWT. In general, changes observed across the assessments were minimal, and did not represent clinically relevant changes over the 12-month treatment period. Of note, there was a decrease in percent of left ventricular mass with amyloid (by cardiac MRI) and some beneficial effect in cardiac autonomic function (improved heart rate variability). When compared to changes in the TRACS study, a relatively smaller increase in NT-proBNP and a slower progression of disease, as assessed by the distance walked in 6MWT, PGA, and SF-36, was observed at 12 months. Changes in echocardiography parameters and KCCQ at 12 months were not clinically relevant.

In summary, outcomes in those patients treated with tafamidis for 12 months appeared somewhat improved compared to patients observed over 12 months without intervention in TRACS. These trends included overall better survival, less CV hospitalisations, stabilisation of cardiac function (as assessed by cardiac biomarkers), results from echocardiographic and cardiac MRI testing, and better functional status.

Patients who successfully completed Study B3461025 could continue into extension Study B3461026, which is an ongoing open label study designed to obtain additional, long-term safety data for tafamidis in patients with ATTR-CM, and to continue to provide patients with 20 mg oral tafamidis soft gelatin

capsule. This extension study is provided in the submission to support the safety profile of tafamidis as part of the All Tafamidis Cohort.

Supportive study B3461045

The objective of this ongoing extension study is long-term safety of tafamidis 20mg and 80mg. See the safety part of this AR.

2.5.3. Discussion on clinical efficacy

The applicant's claimed indication for tafamidis is supported by single pivotal trial.

Design and conduct of clinical studies

Study B3461028 in ATTR-CM patients

This is a phase 3, multicenter, randomised, double-blind, 3-arm, placebo-controlled study in 441 ATTR-CM patients (548 screened, 441 randomised) with a 30-month duration of double-blind treatment.

Subjects were randomised to receive tafamidis 80mg once daily, tafamidis 20mg once daily or placebo with a ratio 2:1:2, in the following manner: n=177 in the placebo arm, n=88 in the tafamidis meglumine 20 mg arm, and n=176 in the tafamidis meglumine 80 mg arm. In this study, tafamidis treatment administered was actually tafamidis "meglumine" (the salt form), which is the already approved VYNDAQEL 20mg, soft capsules (i.e in the arm tafamidis 80mg, 4 capsules of VYNDAQEL 20mg were absorbed once daily in a blinded fashion). However, for practical reasons related to observance, a new formulation was developed later to replace the 4 capsules of VYNDAQEL 20mg by a single claimed as bioequivalent capsule of micronized tafamidis 61mg (the free acid form). This new 61 mg capsule is used in the extension study B3461045, and is proposed for current extension application.

The recommended dose for the claimed cardiac indication is 61 mg once a day. The proposed new formulation (with active substance as an acid) has not been assessed in the pivotal clinical study of 30 month duration, but only in short term PK/PD studies, including the bioequivalence study. However for the dose of 20mg, which was assessed in the 30 month pivotal clinical study, and which is already approved in ATTR-PN indication, the cardiac indication was not claimed by the Applicant.

Regarding the target population, the study was designed to include both types of transthyretin amyloid cardiomyopathy (ATTR-CM): variant and wild-type TTR genotype. Diagnosis and patients' selection were based on the following criteria:

- ≥18 to ≤90 years of age,
- a history of heart failure evidenced by at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) manifested in signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretics for improvement,
- a predominant cardiac phenotype; specifically, documented TTR-CM with either wild-type transthyretin or a variant transthyretin genotype (assessed by genotyping),
- evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm. Since many patients >70 year-old have septal wall thickness >12 mm, notably with increased blood pressure, this criteria of diagnosis is not

sufficient in clinical practice. Echocardiography criteria in accordance with the ESC guidelines is particularly important when restrictive cardiomyopathy or HF with preserved EF is suspected.

- in all patients, the presence of transthyretin amyloid deposits in biopsy tissue obtained from cardiac and noncardiac sites (e.g., fat aspirate, gastrointestinal sites, salivary glands, or bone marrow; amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain). Biopsy is currently rarely performed with a suspicion of ATTR-CM in clinical practice because it is an invasive act. However, a non biopsy approach is now recommended.
- in patients without variant TTR genotype, the presence of TTR precursor protein confirmed by immunohistochemistry or mass spectrometry. Bone scintigraphy was not an inclusion criteria but it is now considered as the most recommended confirmatory test of TTR involvement.
- a plasma NT-proBNP concentration ≥600 pg/mL to ensure patients included in the study have a cardiac cause for their symptoms. BNP should rather have been considered as inclusion criteria in non-acute HF because less sensitive to age and creatinine.
- a 6-minute walk test of >100 m to exclude patients with advanced stage disease (NYHA functional class IV) and patients with a mixed neurologic/cardiac phenotype who may be more likely to experience difficulties completing this test.

Other major exclusion criteria include a confirmed diagnosis of light-chain amyloidosis, heart failure not caused by TTR-CM, history of liver or heart transplantation; implanted cardiac device; eGFR <25 mL/min/1.73m²; BMI <600kg/m²; previous treatment with tafamidis and concurrent treatment with nonsteroidal anti-inflammatory drugs, tauroursodeoxycholate, doxycycline, diflunisal, calcium channel blockers or digitalis.

The demographic characteristics were generally well balanced between groups. The majority of subjects were male (90%), white (80%), wild-type TTR genotype (76%), NYHA Class II (60%), from US (63%) and mean age was 74 years (range: 46 to 89). Other notable groups with fewer patients were non-US (37%), NYHA Class III (32%), variant TTR genotype (24%), black patients (14%). The goal of enrollment of at least 30% of variant TTR genotype patients was not achieved. Additionally, patients with NYHA I were less than 10%. This confirms difficulties to diagnosis NYHA I patients, in particular in the absence of symptoms of heart failure. Therefore, a special attention has been given to results in this patients group in order to identify the clinical relevance of the proposed indication. In addition, an accurate diagnosis cannot be formally established without a number of procedures (biopsy, scinthigraphy…).

The discontinuations rate was high, with a total of 183 patients, and were higher in the placebo group compared to the tafamidis groups (+17.5%): 34.5% vs 52.0%. The most frequent reasons for discontinuation were for 17.5% of patients due to death, 14.1% of patients no longer willing to participate, 6.3% of patients due to adverse events. Regarding patients no longer willing to participate in the study, they were twice more in the placebo group compared to the tafamidis groups (+11.4%): 9.5% vs 20.9%.

The primary analysis used was the method of Finkelstein-Schoenfeld applied to the hierarchical combination of all-cause mortality and frequency of CV-related hospitalisations (defined as the number of times a patient is hospitalised [ie, admitted to a hospital] for CV-related morbidity) during the trial (duration of 30 months), comparing the pooled tafamidis patient group (20 mg and 80 mg dose groups combined) to placebo. The sample size calculation was based on an expected reduction of mortality between 30% and 50%, with a mortality rate in the placebo group of 25%.

Key secondary endpoints were change from Baseline to Month 30 in the 6MWT and the KCCQ-OS score and were controlled for multiplicity.

The remaining secondary and exploratory analyses/endpoints were not adjusted for multiplicity, including CV-related mortality, frequency of CV-related hospitalisation, all-cause mortality, TTR stabilisation at Month 1, change in NT-proBNP concentration. Thus, these endpoints are exploratory and should be interpreted with caution.

The design aspects of the study such as the 2:1:2 randomisation, inclusion of broad baseline disease severity, pooled primary analysis, the use of Finkelstein-Schoenfeld methodology, were discussed within the framework of a scientific advice from the EMA in 2012. The SA given by EMA to the applicant considered that the proposed strategy regarding clinical endpoints was acceptable.

A request for routine GCP inspection has been adopted for this single pivotal study. The Applicant was requested to provide clarifications on the impact of the findings regarding the eligibility of up to 10% of the patients with regards to an echocardiographic inclusion criterion, regarding the adjudication of hospitalisations and regarding biological samples, on the study results. The Applicant justified that these findings had no impact on study results.

Efficacy data and additional analyses

According to the primary analysis performed with the Finkelstein-Schoenfeld method, treatment with tafamidis was superior to placebo over 30 months ($p<0.001$).

All-cause mortality at month 30 was reduced by 30.2% in the tafamidis groups compared to placebo: 29.5% with pooled tafamidis vs 42.9% with placebo, statistically significant ($p=0.0259$). These results are consistent with the expected reduction of mortality between 30% and 50% hypothesized by the Applicant. However, from a clinical point of view, and based on all-cause mortality criteria, the statistically significant differences between groups is observed only after 16 months of treatment.

The frequency of CV-related hospitalizations per year (% of subjects with at least one CV hospitalization) for the ITT analysis set was reduced by 32.3% with pooled tafamidis compared to placebo: 52.3% with tafamidis vs 60.5% with placebo, statistically significant ($p<0.0001$).

In a post hoc analysis, the win ratio (number of pairs of the treated patient wins divided by number of pairs of placebo patient wins) for the primary analysis is 1.695 (95% CI 1.255, 2.289), indicating that a tafamidis-treated patient had a 69.5% higher chance of having a better outcome based on a hierarchical combination of all-cause mortality and CV-related hospitalisation relative to a placebo patient.

Regarding key secondary endpoints, tafamidis reduced, at month 30, the decline in the distance walked during the 6-minute test as compared with placebo (75.68 m [SE, ±9.24; $p<0.001$]) and in the KCCQ-OS score as compared with placebo (13.65 [SE, ±2.13; $p<0.001$]).

The same trend as the primary endpoint was observed for CV-related mortality with a reduction by 30.9% in the tafamidis groups compared to placebo: 20.1% with pooled tafamidis vs 28.2% with placebo, ($p=0.0383$), and a difference between groups observed after 16 months of treatment.

Regarding the secondary endpoint TTR stabilisation at Month 1, significantly more patients in the pooled tafamidis group (86.1%) demonstrated TTR stabilisation than was observed for patients in the placebo group (3.5%), ($p<0.0001$).

The post hoc exploratory endpoint (reduction of NT-proBNP at Month 30) was presented by the Applicant to confirm the favourable effect of tafamidis over placebo ($p=0.0002$).

Regarding the comparison of the 2 dose groups, both doses of tafamidis were superior to placebo over 30 months on the Finkelstein-Schoenfeld primary analysis of all-cause mortality and frequency of CV-related hospitalisations: p=0.0048 with the 20mg and p=0.0030 with the 80mg group.

Furthermore, there was a trend to lower events in the 20mg dose group compared to the 80mg dose group on all the clinical endpoints: all-cause deaths (27.3% with the 20mg vs 30.7% with the 80mg), CV-related hospitalization (47.7% with the 20mg vs 54.5% with the 80mg) and also CV-related deaths (21.6% with the 20mg vs 25.6% with the 80mg). This is confirmed when focusing on the win-ratio of both doses, respectively 1.81 and 1.64 for the 20 mg and 80 mg. Based on these results, it cannot be concluded that the 80mg dose may have more benefit than the 20mg dose.

On the key secondary endpoints, tafamidis 20mg and 80mg were also comparable: significant treatment effects at month 30 on both doses over placebo on the decline in the distance walked during the 6-minute test and the KCCQ-OS score.

Across prespecified subgroups, on TTR genotype and NYHA Class, the difference in all-cause mortality and frequency of CV-related hospitalisations favoured tafamidis over placebo, except in patients with NYHA class III disease at baseline, among whom the rates of CV-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (76.9% vs 58.7%). Also, CV-related mortality (51.3% vs 49.2%) tended to be higher with tafamidis compared to placebo in patients with NYHA class III.

Further analyses according to the doses and time course are necessary to better characterise the effect of tafamidis, notably in more severe patients who may not benefit from this treatment. Regarding the issue of tafamidis efficacy between older and younger patients, consistent results are observed for both the 20 mg and 80 mg doses in all patients, above and below the median age of 75 years.

Results on TTR stabilisation between 20mg and 80mg are comparable: 82.7% and 87.8%, with no significant difference between groups. No benefit of the 80mg over the 20mg dose can be claimed based on these analyses. This is consistent with the primary efficacy results.

Less TTR stabilization in variant patients than in wild patients is observed: 58.9% and 94.2%.

An exploratory analysis of the NT-proBNP concentrations was provided by the Applicant. From a methodological point of view, such post-hoc analysis, without predefined hypothesis and sample size calculation, cannot be endorsed. Furthermore, NT-proBNP has questionable clinical value in this study, since no validated values directly correlated to clinical improvement exist with the observed values in this study: LS mean of 1185 pg/ml with 20mg and 633 pg/ml with 80mg at month 12 and 2542.23 pg/ml with 20mg and 1371.71 pg/ml with 80mg at month 30, making the distinction between 20mg and 80mg not really clear. For the same reasons, the results on troponin I could not be considered sufficiently relevant to distinguish both doses.

The supportive studies B3461025 and B3461045 are consistent with the results of study B3461028, since no increase in mortality is observed with either the 20mg or 80mg doses. However, they do not allow any comparison between the efficacy of the 20mg and the 80mg doses, contrary to the Applicant claim that all-cause mortality is reduced on the 80mg dose relative to the 20mg in study B3461045.

2.5.4. Conclusions on the clinical efficacy

Overall, tafamidis has clearly demonstrated consistent efficacy across the primary, key secondary and other secondary endpoints for both tafamidis meglumine 20 mg and 80 mg doses. Regarding the comparison of the 2 dose groups, both doses of tafamidis were superior to placebo over 30 months on the primary analysis of all-cause mortality and frequency of CV-related hospitalisations: p=0.0048 with

the 20mg and p=0.0030 with the 80mg group. The 61 mg is considered effective in the requested indication.

Although the MAH did not apply for an approval of the ATTR CM indication for the 20mg dose, the MAH was, based on the similar effects shown for this lower dose, asked to justify the dose selection and possible appropriateness of use of the 20mg. However, this point has not been fully understood.

The MAH has not provided fully convincing arguments to select 61 mg (80 mg equivalent) dose as compared to 20 mg regarding hard parameters of clinical efficacy. The selected approach regarding NT-proBNP and the other PK parameters related to TTR stabilization and fostered outcomes are not in line with what has been clinically observed in study B3461028. However, the 80 mg dose has the largest evidence base that is twice as large than for the 20 mg dose. Moreover, tafamidis was similarly well tolerated across both dose groups.

Therefore, considering also that there are no clear biomarker target levels, signs, or symptoms to steer dosing and the therapy has shown morbi/mortality benefit it is agreed that the 61mg dose is an appropriate dose in this particular context of severe and evolutive disease. The benefit-risk balance of the 61 mg dose was considered positive for the following agreed indication:

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

- Regarding the assessment tools for diagnosis:

The severity of the disease can be distinguished between the variant and the wild-type forms. Indeed, when considering the mechanism of the disease, variant TTR is inherited by mutation in hereditary forms, while in wild-type forms, TTR is becoming unstable with age, without clear origin. Variant forms can be detected earlier, in a family context, even before the onset of cardiac symptoms, and can be associated with neurologic phenotype. Wild-type patients are around 75 year-old at diagnosis and are also associated with multiple non-cardiac symptoms such as deafness, carpa tunnel syndrome or lumbar canal stenosis, and may be common in the elderly population (>80-85 year-old). It seems that the evolution of the disease differs between these 2 types, with median survival of 25.6 months for variants and 43.0 months for wild-type.

Consequently, since the medical need may not be the same, with a more severe and evolutive disease in the variant patients, the management of patients may differ. It is specified in section 4.2 of the SmPC that the etiologic diagnosis must be done by a physician knowledgeable in the management of amyloidosis or cardiomyopathy to confirm ATTR-CM and exclude AL amyloidosis before starting tafamidis, using appropriate assessment tools such as: bone scintigraphy and blood/urine assessment, and/or histological assessment by biopsy, and transthyretin (TTR) genotyping to characterise as wild-type or hereditary.

The HealthCare Professional Guide (HCP Guide) was updated with key message on the clinical criteria for the diagnosis of ATTR-CM in the Healthcare Professional Guide. The THAOS Protocol is in the process of being amended. This will be submitted as a PASS protocol amendment early 2020.

2.6. Clinical safety

Patient exposure

Table 6: Number of Treated Patients (Total Patient-Years of Exposure)

	Number of Treated Patients (Total Patient-Years of Exposure)			
Cohort	**Placebo**	**Tafamidis 20 mg**	**Tafamidis 80 mg**	**Pooled Tafamidis (20 mg + 80 mg)**
B3461028	177 (324.36)	88 (179.26)	176 (348.92)	264 (528.18)
Broad (B3461028 and B3461045)	-	115 (214.74)	227 (415.44)	342 (630.18)
All Tafamidis (B3461028, B3461045, B3461025 and B3461026)	-	150 (354.96)	227 (415.44)	377 (770.40)

Source: Module 5.3.5.3 B3461028 Cohort Safety Table 2.2.1.a (Placebo); All Tafamidis Cohort Safety Table 1.1.1.

Table 7: Study Drug Exposure - B3461028 Cohort

	Placebo (N=177)	**Tafamidis 20 mg (N=88)**	**Tafamidis 80 mg (N=176)**	**Tafamidis 20 mg + 80 mg (N=264)**
Duration of treatment (months)[a]				
N	177	88	176	264
Mean (SD)	22.0 (9.66)	24.4 (9.35)	23.8 (9.59)	24.0 (9.49)
Median	27.9	29.7	29.8	29.7
Range	(0.5, 30.6)	(0.6, 30.9)	(0.3, 30.6)	(0.3, 30.9)
Duration category (months) n (%)				
<6 month	17 (9.6)	9 (10.2)	13 (7.4)	22 (8.3)
6 - <12 month	17 (9.6)	3 (3.4)	19 (10.8)	22 (8.3)
12 - <18 month	21 (11.9)	8 (9.1)	14 (8.0)	22 (8.3)
18 - <24 month	24 (13.6)	4 (4.5)	11 (6.3)	15 (5.7)
24 - <30 month	60 (33.9)	37 (42.0)	54 (30.7)	91 (34.5)
30 - <36 month	38 (21.5)	27 (30.7)	65 (36.9)	92 (34.8)
Total amount of tafamidis (mg)[b]				
N		88	176	264
Mean (SD)		14880.5 (5688.97)	57929.1 (23340.22)	43579.5 (28045.99)
Median		18080.0	72600.0	39960.0
Range		(380.0, 18820.0)	(640.0, 74480.0)	(380.0, 74480.0)

Source: Module 5.3.5.3 B3461028 Cohort Safety Table 13.1.a
[a]: Duration of treatment = (last date of study drug dosing – first date of study drug dosing + 1)/30.4375.
[b]: Total amount of tafamidis (mg) = duration of treatment (days)* 20 mg/80 mg. Placebo patients did not receive tafamidis and therefore this variable is not applicable for that group.

Table 8: Dosing Compliance - B3461028 Cohort

	Placebo (N=177) n (%)	**Tafamidis 20 mg (N=88) n (%)**	**Tafamidis 80 mg (N=176) n (%)**	**Tafamidis 20 mg + 80 mg (N=264) n (%)**
Overall				
<80%	5 (2.8)	4 (4.5)	3 (1.7)	7 (2.7)
80 – <90%	2 (1.1)	2 (2.3)	6 (3.4)	8 (3.0)
≥90%	161 (91.0)	78 (88.6)	158 (89.8)	236 (89.4)

Source: Module 5.3.5.3 B3461028 Cohort Safety Table 13.2.a
Compliance is defined as the total number of tablets actually taken by a subject divided by the number of tablets expected to be taken over treatment period times 100%.
Only those safety analysis subjects for whom adherence data was available and calculable are used in generating adherence statistics.

Table 9: Study Drug Exposure - Broad Cohort

	Tafamidis 20 mg (N=115)	Tafamidis 80 mg (N=227)
Duration of treatment (months)[a]		
N	115	227
Mean (SD)	22.4 (14.10)	22.0 (14.28)
Median	30.0	28.6
Range	(0.0, 46.8)	(0.0, 49.4)
Duration category (months) n(%)		
<6 month	24 (20.9)	47 (20.7)
6 - <12 month	13 (11.3)	35 (15.4)
12 - <18 month	10 (8.7)	15 (6.6)
18 - <24 month	4 (3.5)	11 (4.8)
24 - <30 month	7 (6.1)	12 (5.3)
30 - <36 month	38 (33.0)	69 (30.4)
36 - <42 month	16 (13.9)	30 (13.2)
≥42 month	3 (2.6)	8 (3.5)
Total amount of tafamidis (mg)[b]		
N	115	227
Mean (SD)	13640.5 (8585.71)	53477.0 (34760.11)
Median	18260.0	69600.0
Range	(20.0, 28460.0)	(80.0, 120400.0)

Source: Module 5.3.5.3 Broad Cohort Safety Table 13.1.b
Broad Cohort includes tafamidis exposure from studies B3461028 and B3461045 excluding placebo exposure in B3461028.
[a]: Duration of treatment = (last date of study drug dosing – first date of study drug dosing + 1)/30.4375 by excluding the gap between parent and extension.
[b]: Total amount of tafamidis (mg) = duration of treatment (days)* 20 mg/80 mg.

Table 10: Dosing Compliance – Broad Cohort

	Tafamidis 20 mg (N=115) n (%)	Tafamidis 80 mg (N=227) n (%)
Overall		
<80%	5 (4.3)	4 (1.8)
80 – <90%	4 (3.5)	7 (3.1)
≥90%	93 (80.9)	185 (81.5)

Source: Module 5.3.5.3 Broad Cohort Safety Table 13.2.b
Broad Cohort includes tafamidis exposure from studies B3461028 and B3461045 excluding placebo exposure in B3461028.
Compliance is defined as the total number of tablets actually taken by a subject divided by the number of tablets expected to be taken over treatment period times 100%.
Only those safety analysis subjects for whom adherence data was available and calculable are used in generating adherence statistics.

Adverse events

Table 11

Table 31. Treatment-Emergent Adverse Events (Safety Analysis Set)

	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Pooled Tafamidis (N=264) n (%)	Placebo (N=177) n (%)
Treatment-emergent AEs (all causalities)				
Number of TEAEs	1036	2138	3174	2463
Subjects with TEAEs	87 (98.9)	173 (98.3)	260 (98.5)	175 (98.9)
Subjects with treatment-emergent SAEs	66 (75.0)	133 (75.6)	199 (75.4)	140 (79.1)
Subjects with severe TEAEs	54 (61.4)	110 (62.5)	164 (62.1)	114 (64.4)
Subjects discontinued drug due to TEAEs	16 (18.2)	40 (22.7)	56 (21.2)	51 (28.8)
Subjects with dose reduced due to TEAEs	0	2 (1.1)	2 (0.8)	4 (2.3)
Subjects with temporary discontinuation due to TEAEs	20 (22.7)	33 (18.8)	53 (20.1)	46 (26.0)
Treatment-emergent AEs (treatment-related)				
Number of TEAEs	67	226	293	207
Subjects with TEAEs	34 (38.6)	79 (44.9)	113 (42.8)	90 (50.8)
Subjects with treatment-emergent SAEs	2 (2.3)	3 (1.7)	5 (1.9)	4 (2.3)
Subjects with severe TEAEs	3 (3.4)	5 (2.8)	8 (3.0)	5 (2.8)
Subjects discontinued drug due to TEAEs	0	1 (0.6)	1 (0.4)	3 (1.7)
Subjects with dose reduced due to TEAEs	0	2 (1.1)	2 (0.8)	3 (1.7)
Subjects with temporary discontinuation due to TEAEs	2 (2.3)	5 (2.8)	7 (2.7)	7 (4.0)

Table 12

Table 32. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (All Causalities) with PT ≥5% Incidence By Dose (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
Subjects with any TEAEs	87 (98.9)	167 (94.9)	172 (97.2)
Blood and lymphatic system disorders	6 (6.8)	11 (6.3)	13 (7.3)
Anaemia	6 (6.8)	11 (6.3)	13 (7.3)
Cardiac disorders	53 (60.2)	97 (55.1)	109 (61.6)
Atrial fibrillation	16 (18.2)	35 (19.9)	33 (18.6)
Atrial flutter	7 (8.0)	10 (5.7)	15 (8.5)
Cardiac failure	30 (34.1)	46 (26.1)	60 (33.9)
Cardiac failure acute	4 (4.5)	24 (13.6)	17 (9.6)
Cardiac failure congestive	17 (19.3)	22 (12.5)	33 (18.6)
Ventricular tachycardia	3 (3.4)	7 (4.0)	13 (7.3)
Endocrine disorders	5 (5.7)	12 (6.8)	10 (5.6)
Hypothyroidism	5 (5.7)	12 (6.8)	10 (5.6)
Eye disorders	3 (3.4)	9 (5.1)	2 (1.1)
Cataract	3 (3.4)	9 (5.1)	2 (1.1)
Gastrointestinal disorders	39 (44.3)	71 (40.3)	87 (49.2)
Abdominal distension	6 (6.8)	7 (4.0)	5 (2.8)
Abdominal pain	6 (6.8)	9 (5.1)	8 (4.5)
Ascites	7 (8.0)	6 (3.4)	9 (5.1)
Constipation	14 (15.9)	26 (14.8)	30 (16.9)
Diarrhoea	10 (11.4)	22 (12.5)	39 (22.0)
Gastrooesophageal reflux disease	6 (6.8)	0	7 (4.0)
Inguinal hernia	5 (5.7)	6 (3.4)	3 (1.7)
Nausea	9 (10.2)	20 (11.4)	36 (20.3)
Vomiting	7 (8.0)	7 (4.0)	16 (9.0)
General disorders and administration site conditions	43 (48.9)	82 (46.6)	87 (49.2)
Asthenia	11 (12.5)	18 (10.2)	11 (6.2)
Chest discomfort	3 (3.4)	9 (5.1)	9 (5.1)
Chest pain	5 (5.7)	11 (6.3)	10 (5.6)
Fatigue	16 (18.2)	29 (16.5)	33 (18.6)
Gait disturbance	4 (4.5)	4 (2.3)	11 (6.2)
Oedema	7 (8.0)	11 (6.3)	20 (11.3)
Oedema peripheral	17 (19.3)	30 (17.0)	31 (17.5)
Peripheral swelling	2 (2.3)	6 (3.4)	9 (5.1)
Infections and infestations	41 (46.6)	84 (47.7)	82 (46.3)
Bronchitis	9 (10.2)	21 (11.9)	19 (10.7)
Cellulitis	6 (6.8)	8 (4.5)	12 (6.8)
Influenza	4 (4.5)	9 (5.1)	8 (4.5)
Nasopharyngitis	7 (8.0)	14 (8.0)	17 (9.6)
Pneumonia	10 (11.4)	23 (13.1)	17 (9.6)
Sinusitis	5 (5.7)	10 (5.7)	1 (0.6)
Upper respiratory tract infection	7 (8.0)	17 (9.7)	16 (9.0)
Urinary tract infection	9 (10.2)	16 (9.1)	27 (15.3)
Injury, poisoning and procedural complications	30 (34.1)	48 (27.3)	41 (23.2)
Contusion	6 (6.8)	11 (6.3)	5 (2.8)
Fall	27 (30.7)	43 (24.4)	41 (23.2)
Investigations	23 (26.1)	42 (23.9)	51 (28.8)
Blood creatinine increased	3 (3.4)	9 (5.1)	8 (4.5)

Table 32. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (All Causalities) with PT ≥5% Incidence By Dose (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
Gamma-glutamyltransferase increased	3 (3.4)	9 (5.1)	11 (6.2)
International normalised ratio increased	5 (5.7)	4 (2.3)	5 (2.8)
Venous pressure jugular increased	4 (4.5)	4 (2.3)	9 (5.1)
Weight decreased	6 (6.8)	8 (4.5)	18 (10.2)
Weight increased	7 (8.0)	13 (7.4)	12 (6.8)
Metabolism and nutrition disorders	40 (45.5)	69 (39.2)	101 (57.1)
Decreased appetite	8 (9.1)	14 (8.0)	25 (14.1)
Dehydration	3 (3.4)	5 (2.8)	9 (5.1)
Fluid overload	13 (14.8)	19 (10.8)	29 (16.4)
Fluid retention	5 (5.7)	6 (3.4)	16 (9.0)
Gout	10 (11.4)	18 (10.2)	29 (16.4)
Hyperkalaemia	1 (1.1)	11 (6.3)	13 (7.3)
Hyperuricaemia	3 (3.4)	9 (5.1)	7 (4.0)
Hypokalaemia	8 (9.1)	16 (9.1)	19 (10.7)
Hyponatraemia	2 (2.3)	12 (6.8)	13 (7.3)
Musculoskeletal and connective tissue disorders	35 (39.8)	73 (41.5)	74 (41.8)
Arthralgia	8 (9.1)	18 (10.2)	21 (11.9)
Back pain	9 (10.2)	17 (9.7)	24 (13.6)
Muscle spasms	10 (11.4)	15 (8.5)	14 (7.9)
Muscular weakness	2 (2.3)	5 (2.8)	13 (7.3)
Musculoskeletal pain	3 (3.4)	13 (7.4)	11 (6.2)
Myalgia	5 (5.7)	5 (2.8)	2 (1.1)
Neck pain	5 (5.7)	3 (1.7)	5 (2.8)
Osteoarthritis	2 (2.3)	9 (5.1)	9 (5.1)
Pain in extremity	6 (6.8)	27 (15.3)	20 (11.3)
Nervous system disorders	30 (34.1)	57 (32.4)	64 (36.2)
Balance disorder	2 (2.3)	15 (8.5)	2 (1.1)
Carpal tunnel syndrome	5 (5.7)	5 (2.8)	4 (2.3)
Dizziness	17 (19.3)	25 (14.2)	37 (20.9)
Headache	1 (1.1)	9 (5.1)	11 (6.2)
Hypoaesthesia	5 (5.7)	4 (2.3)	6 (3.4)
Neuropathy peripheral	5 (5.7)	3 (1.7)	12 (6.8)
Syncope	5 (5.7)	11 (6.3)	16 (9.0)
Psychiatric disorders	17 (19.3)	26 (14.8)	27 (15.3)
Depression	6 (6.8)	7 (4.0)	8 (4.5)
Insomnia	12 (13.6)	20 (11.4)	22 (12.4)
Renal and urinary disorders	24 (27.3)	40 (22.7)	62 (35.0)
Acute kidney injury	12 (13.6)	17 (9.7)	29 (16.4)
Haematuria	10 (11.4)	10 (5.7)	17 (9.6)
Renal failure	5 (5.7)	10 (5.7)	9 (5.1)
Renal impairment	3 (3.4)	6 (3.4)	9 (5.1)
Urinary retention	2 (2.3)	7 (4.0)	13 (7.3)
Reproductive system and breast disorders	4 (4.5)	9 (5.1)	6 (3.4)
Gynaecomastia	4 (4.5)	9 (5.1)	6 (3.4)
Respiratory, thoracic and mediastinal disorders	44 (50.0)	57 (32.4)	93 (52.5)
Cough	16 (18.2)	21 (11.9)	30 (16.9)
Dyspnoea	21 (23.9)	29 (16.5)	55 (31.1)
Dyspnoea exertional	5 (5.7)	10 (5.7)	14 (7.9)

Table 32. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (All Causalities) with PT ≥5% Incidence By Dose (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
Epistaxis	3 (3.4)	13 (7.4)	15 (8.5)
Pleural effusion	12 (13.6)	14 (8.0)	32 (18.1)
Skin and subcutaneous tissue disorders	7 (8.0)	18 (10.2)	25 (14.1)
Pruritus	4 (4.5)	12 (6.8)	15 (8.5)
Rash	3 (3.4)	6 (3.4)	12 (6.8)
Vascular disorders	14 (15.9)	28 (15.9)	24 (13.6)
Hypotension	12 (13.6)	19 (10.8)	19 (10.7)
Orthostatic hypotension	2 (2.3)	9 (5.1)	6 (3.4)

Source: Table 14.3.1.2.3.3.1

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects;

n = number of subjects; TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of subjects in the safety analysis set. Multiple occurrences of the same adverse event in a subject at the preferred term level or system organ class level are counted as 1 adverse event per treatment in each row. Includes events occurring up to 28 days after last dose of study drug.

MedDRA Version 20.1 coding dictionary applied.

Table 13

N = Number of subjects treated by period and by arm n = number of subjects with **cardiac failure acute**					
	Treatment <6 months	Treatment 6 to <12 months	Treatment 12 to <18 months	Treatment 18 to <24 months	Treatment ≥ 24 months
Placebo	N=177 2 (1,1%)	N=160 5 (3,1%)	N=143 3 (2,1%)	N=122 2 (1,6%)	N=98 5 (5,1%)
Tafamidis 20mg	N=88 1 (1,1%)	N=79 1 (1,3%)	N=76 1 (1,3%)	N=68 1 (1,5%)	N=64 0 (0%)
Tafamidis 80mg	N=176 6 (3,4%)	N=163 6 (3,7%)	N=144 4 (2,8%)	N=130 2 (1,5%)	N=119 6 (5%)

Table 26. Tafamidis PF-06291826 - Integrated Summary of Safety B3461028 Cohort Treatment-Emergent Adverse Events (Treatment related)

	Placebo	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis 20 mg + 80 mg
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects evaluable for adverse events	177	88	176	264
Number of adverse events	207	67	226	293
Subjects with adverse events	90 (50.8)	34 (38.6)	79 (44.9)	113 (42.8)
Subjects with serious adverse events	4 (2.3)	2 (2.3)	3 (1.7)	5 (1.9)
Subjects with severe adverse events	5 (2.8)	3 (3.4)	5 (2.8)	8 (3.0)
Subjects discontinued due to adverse event	3 (1.7)	0	1 (0.6)	1 (0.4)
Subjects with dose reduced due to adverse events	3 (1.7)	0	2 (1.1)	2 (0.8)
Subjects with temporary discontinuation due to adverse events	7 (4.0)	2 (2.3)	5 (2.8)	7 (2.7)

Table 14

Table 15

Table 33. Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Treatment Related) with PT ≥5% Incidence by Dose (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 (n%)	Tafamidis 80 mg N=176 (n%)	Placebo N=177 (n%)
Gastrointestinal disorders	3 (3.4)	22 (12.5)	26 (14.7)
Diarrhoea	2 (2.3)	14 (8.0)	18 (10.2)
Nausea	1 (1.1)	10 (5.7)	10 (5.6)
Infections and infestations	5 (5.7)	4 (2.3)	8 (4.5)
Urinary tract infection	5 (5.7)	4 (2.3)	8 (4.5)

Source: Table 14.3.1.3.3.3.1

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term;

TEAE = Treatment-Emergent Adverse Event

Notes: Percentages are based on the number of subjects in the Safety Analysis Set. Multiple occurrences of the same adverse event in a subject at the preferred term level or system organ class level are counted as 1 adverse event per treatment in each row. Includes events occurring up to 28 days after last dose of study drug.

MedDRA Version 20.1 coding dictionary applied.

Table 16

	Placebo N=177			**Tafamidis 20mg N=88**			**Tafamidis 80mg N=176**		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Any adverse events	56 (31,6%)	29 (16,4%)	5 (2,8%)	16 (18.2%)	15 (17%)	3 (3.4%)	49 (27.8%)	25 (14.2%)	5 (2.8%)

Serious adverse event/deaths/other significant events

Table 17

Table 34. Summary of Deaths and Cardiovascular Mortality (Safety Analysis Set)

	Tafamidis 20 mg N=88 n (%)	**Tafamidis 80 mg N=176 n (%)**	**Placebo N=177 n (%)**	**Total N=441 n (%)**
Deaths (all causes)	23 (26.1)	49 (27.8)	72 (40.7)	144 (32.7)
Deaths during Study Period	14 (15.9)	25 (14.2)	38 (21.5)	77 (17.5)
Deaths during Follow-up period	9 (10.2)	24 (13.6)	34 (19.2)	67 (15.2)
Cause of Death[a]				
Disease under study	17 (19.3)	28 (15.9)	49 (27.7)	94 (21.3)
Unknown	1 (1.1)	4 (2.3)	3 (1.7)	8 (1.8)
Other	5 (5.7)	17 (9.7)	20 (11.3)	42 (9.5)
Number of cardiovascular-related deaths[b]	18 (20.5)	40 (22.7)	60 (33.9)	118 (26.8)
Cardiovascular mortality				
Number of heart transplants[c]	1 (1.1)	6 (3.4)	4 (2.3)	11 (2.5)
Number of cardiac mechanical assist devices	0	2 (1.1)	0	2 (0.5)

Table 35. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (All Causalities) with PT ≥5% Incidence by Dose - ARGUS Data (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
Subjects with any serious TEAE	47 (53.4)	94 (53.4)	104 (58.8)
Cardiac disorders	33 (37.5)	70 (39.8)	81 (45.8)
Atrial fibrillation	7 (8.0)	11 (6.3)	8 (4.5)
Cardiac failure	16 (18.2)	34 (19.3)	40 (22.6)
Cardiac failure acute	4 (4.5)	23 (13.1)	17 (9.6)
Cardiac failure congestive	14 (15.9)	21 (11.9)	31 (17.5)
General disorders and administration site conditions	22 (25.0)	49 (27.8)	65 (36.7)
Condition aggravated	21 (23.9)	40 (22.7)	58 (32.8)
Disease progression	5 (5.7)	13 (7.4)	12 (6.8)
Infections and infestations	6 (6.8)	13 (7.4)	12 (6.8)
Pneumonia	6 (6.8)	13 (7.4)	12 (6.8)
Injury, poisoning and procedural complications	5 (5.7)	9 (5.1)	5 (2.8)
Fall	5 (5.7)	9 (5.1)	5 (2.8)
Nervous system disorders	0	6 (3.4)	10 (5.6)
Syncope	0	6 (3.4)	10 (5.6)
Renal and urinary disorders	9 (10.2)	13 (7.4)	15 (8.5)
Acute kidney injury	9 (10.2)	13 (7.4)	15 (8.5)
Respiratory, thoracic and mediastinal disorders	5 (5.7)	6 (3.4)	4 (2.3)
Pleural effusion	5 (5.7)	6 (3.4)	4 (2.3)

Table 18

Table 19

Table 36. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Treatment Related) by Dose - ARGUS Data (Safety Analysis Set)

System Organ Class Preferred Term	Tafamidis 20 mg N=88 n (%)	Tafamidis 80 mg N=176 n (%)	Placebo N=177 n (%)
Subjects with any serious TEAE	5 (5.7)	7 (4.0)	12 (6.8)
Blood and lymphatic system disorders	1 (1.1)	0	0
Coagulopathy	1 (1.1)	0	0
Cardiac disorders	2 (2.3)	0	4 (2.3)
Atrioventricular block	1 (1.1)	0	0
Bradycardia	1 (1.1)	0	0
Cardiac failure congestive	0	0	2 (1.1)
Ventricular fibrillation	0	0	1 (0.6)
Ventricular tachycardia	0	0	1 (0.6)
Gastrointestinal disorders	1 (1.1)	2 (1.1)	0
Gastritis	1 (1.1)	0	0
Haematochezia	0	1 (0.6)	0
Pancreatitis	0	1 (0.6)	0
General disorders and administration site conditions	0	0	1 (0.6)
Disease progression	0	0	1 (0.6)
Infections and infestations	0	3 (1.7)	0
Clostridium difficile colitis	0	1 (0.6)	0
Lower respiratory tract infection	0	1 (0.6)	0
Urinary tract infection	0	1 (0.6)	0
Investigations	0	1 (0.6)	0
Liver function test increased	0	1 (0.6)	0
Metabolism and nutrition disorders	0	1 (0.6)	2 (1.1)
Hyperkalaemia	0	1 (0.6)	1 (0.6)
Hypovolaemia	0	0	1 (0.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (0.6)
Gallbladder adenocarcinoma	0	0	1 (0.6)
Nervous system disorders	0	0	2 (1.1)
Dizziness	0	0	1 (0.6)
Lethargy	0	0	1 (0.6)
Loss of consciousness	0	0	1 (0.6)
Psychiatric disorders	0	0	1 (0.6)
Mental status changes	0	0	1 (0.6)
Renal and urinary disorders	1 (1.1)	0	2 (1.1)
Acute kidney injury	1 (1.1)	0	2 (1.1)
Respiratory, thoracic and mediastinal disorders	0	0	3 (1.7)
Dyspnoea	0	0	1 (0.6)
Pulmonary oedema	0	0	1 (0.6)
Pulmonary toxicity	0	0	1 (0.6)
Vascular disorders	0	0	1 (0.6)
Hypotension	0	0	1 (0.6)

Laboratory findings

Table 20 and Table 21

Table 57. Number and Percent of Subjects with Treatment-Emergent Potentially Clinically Significant (PCS) Laboratory Results in the Healthy Subjects (HV Cohort) Treated with Tafamidis Versus Placebo

Analyte	PCS Criteria	Tafamidis n = 300 no. (%)	Placebo n = 71 no. (%)
Electrolytes			
Phosphate	High [>5.3 MG/DL]	4 (1.3)	0
Potassium	High [>6 MEQ/L]	1 (0.3)	1 (1.4)
Haematology			
Haematocrit	Low [Male<37 %, Female<32 %]	1 (0.3)	0
Neutrophils (absolute)	Low [<1.5 10^3//MM^3]	8 (2.7)	1 (1.4)
White blood cell	Low [<2.8 10^3/MM^3]	1 (0.3)	0
Hormones			
Free T4 (Thyroxine)	Low [<0.7 NG/DL]	5 (1.7)	2 (2.8)
Thyroid stimulating hormone	High [>5 UIU/ML]	3 (1.0)	0
	Low [<0.3 UIU/ML]	4 (1.3)	1 (1.4)
Thyroxine (Total)	Low [<3.98 UG/DL]	3 (1.0)	2 (2.8)
Lipids			
Cholesterol	High [>300 MG/DL]	1 (0.3)	0
Liver function			
Aspartate aminotransferase	High [>3xULN IU/L]	1 (0.3)	0
Total bilirubin	High [>1.98 MG/DL]	2 (0.7)	0
Renal function			
Blood urea nitrogen	High [>27.63 MG/DL]	3 (1.0)	0

Source: Module 5.3.5.3 HV Cohort Safety Table 39
Includes protocols: B3461015, B3461012, B3461014, B3461017, B3461013, B3461018, B3461009, B3461030, B3461031, B3461040, B3461044, B3461050, B3461051, B3461052, and B3461053.
Subject counts are not mutually exclusive.
Abbreviations: n = sample size; no. = number of subjects; PCS = potentially clinically significant; T4 = thyroxine; UIU = micro international unit.

Table 49. Treatment Related Hepatic Events by System Organ Class and Preferred Term

Number of Subjects Evaluable for AEs Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Placebo (N=177) n (%)	Tafamidis 20 mg (N=88) n (%)	Tafamidis 80 mg (N=176) n (%)	Tafamidis 20 mg + 80 mg (N=264) n (%)
HEPATOBILIARY DISORDERS				
Cholestasis	1 (0.6)	0	1 (0.6)	1 (0.4)
Hepatic congestion	0	0	2 (1.1)	2 (0.8)
Hyperbilirubinaemia	2 (1.1)	0	0	0
Jaundice cholestatic	0	0	1 (0.6)	1 (0.4)
INVESTIGATIONS				
Alanine aminotransferase increased	1 (0.6)	0	0	0
Aspartate aminotransferase increased	1 (0.6)	0	1 (0.6)	1 (0.4)
Blood bilirubin increased	0	3 (3.4)	0	3 (1.1)
Gamma-glutamyltransferase increased	5 (2.8)	2 (2.3)	6 (3.4)	8 (3.0)
Hepatic enzyme increased	1 (0.6)	0	0	0
International normalised ratio increased	0	1 (1.1)	1 (0.6)	2 (0.8)
Liver function test abnormal	2 (1.2)	0	0	0
Liver function test increased	1 (0.6)	0	6 (3.4)	6 (2.3)
Prothrombin time prolonged	0	0	1 (0.6)	1 (0.4)
Transaminases increased	1 (0.6)	0	0	0

Source: Module 5.3.5.3 Cohort B3461028 Table 4.7.2.a

Table 22

Table 37. Incidence of Laboratory Test Abnormalities (Normal Baseline) - By Dose (Safety Analysis Set)

Number of Subjects Evaluable for Laboratory Abnormalities Number (%) with Laboratory Abnormalities				Tafamidis 20 mg 88 63 (71.6)		Tafamidis 80 mg 176 128 (72.7)		Placebo 177 123 (69.5)	
Group	Parameter	Units	Criteria	N	n (%)	N	n (%)	N	n (%)
Chemistry	Albumin	G/DL	<0.8 x LLN	83	1 (1.2)	170	2 (1.2)	169	3 (1.8)
			>1.2 x ULN	83	0	170	0	169	0
	Bicarbonate	MEQ/L	<0.9 x LLN	86	0	171	3 (1.8)	173	1 (0.6)
			>1.1 x ULN	86	2 (2.3)	171	2 (1.2)	173	1 (0.6)
	Calcium	MG/DL	<0.9 x LLN	87	0	173	0	170	0
			>1.1 x ULN	87	0	173	0	170	1 (0.6)
	Chloride	MEQ/L	<0.9 x LLN	77	2 (2.6)	160	5 (3.1)	163	7 (4.3)
			>1.1 x ULN	77	0	160	0	163	0
	Glucose	MG/DL	<0.6 x LLN	52	0	115	0	105	1 (1.0)
			>1.5 x ULN	52	4 (7.7)	115	12 (10.4)	105	15 (14.3)
	Phosphate	MG/DL	<0.8 x LLN	87	0	175	0	176	0
			>1.2 x ULN	87	0	175	1 (0.6)	176	1 (0.6)
	Potassium	MEQ/L	<0.9 x LLN	84	5 (6.0)	170	10 (5.9)	166	15 (9.0)
			>1.1 x ULN	84	1 (1.2)	170	1 (0.6)	166	0
	Protein	G/DL	<0.8 x LLN	83	2 (2.4)	167	0	166	1 (0.6)
			>1.2 x ULN	83	0	167	0	166	0
	Retinol Binding Protein	MG/DL	>ULN	58	24 (41.4)	104	26 (25.0)	107	36 (33.6)
	Sodium	MEQ/L	<0.95 x LLN	75	5 (6.7)	165	9 (5.5)	161	7 (4.3)
			>1.05 x ULN	75	0	165	0	161	0
	Thyrotropin	UIU/ML	<0.8 x LLN	80	1 (1.3)	155	12 (7.7)	167	7 (4.2)
			>1.2 x ULN	80	8 (10.0)	155	15 (9.7)	167	26 (15.6)
	Thyroxine	UG/DL	<0.8 x LLN	81	10 (12.3)	157	47 (29.9)	157	7 (4.5)
			>1.2 x ULN	81	0	157	0	157	2 (1.3)
	Free Thyroxine	NG/DL	<0.8 x LLN	68	0	124	1 (0.8)	132	2 (1.5)
			>1.2 x ULN	68	7 (10.3)	124	14 (11.3)	132	24 (18.2)
Hematology	Mean Corpuscular Hemoglobin	PG	<0.9 x LLN	80	1 (1.3)	169	1 (0.6)	164	1 (0.6)
			>1.1 x ULN	80	0	169	0	164	0
	Mean Corpuscular Volume	10^{-15}L	<0.9 x LLN	78	0	160	1 (0.6)	154	0
			>1.1 x ULN	78	1 (1.3)	160	1 (0.6)	154	0
	Leukocytes	10^3/MM^3	<0.6 x LLN	84	0	164	1 (0.6)	161	0
			>1.5 x ULN	84	0	164	0	161	0
	Lymphocytes	10^3/MM^3	<0.8 x LLN	72	3 (4.2)	157	18 (11.5)	156	23 (14.7)

PFIZER CONFIDENTIAL

Table 37. Incidence of Laboratory Test Abnormalities (Normal Baseline) - By Dose (Safety Analysis Set)

Number of Subjects Evaluable for Laboratory Abnormalities Number (%) with Laboratory Abnormalities				Tafamidis 20 mg 88 63 (71.6)		Tafamidis 80 mg 176 128 (72.7)		Placebo 177 123 (69.5)	
Group	Parameter	Units	Criteria	N	n (%)	N	n (%)	N	n (%)
			>1.2 x ULN	72	0	157	0	156	2 (1.3)
	Neutrophils	10^3/MM^3	<0.8 x LLN	85	1 (1.2)	159	3 (1.9)	162	1 (0.6)
			>1.2 x ULN	85	3 (3.5)	159	5 (3.1)	162	7 (4.3)
	Platelets	10^3/MM^3	<0.5 x LLN	75	0	159	0	158	1 (0.6)
			>1.75 x ULN	75	0	159	0	158	0
Urinalysis	Ketones		≥1	79	3 (3.8)	160	3 (1.9)	164	3 (1.8)
	Nitrite		≥1	80	3 (3.8)	156	5 (3.2)	163	8 (4.9)
	Urine Bilirubin		≥1	75	6 (8.0)	152	16 (10.5)	154	7 (4.5)
	Urine Blood (free Hb)		≥1	74	18 (24.3)	145	21 (14.5)	159	44 (27.7)
	Urine Glucose		≥1	81	1 (1.2)	162	2 (1.2)	164	5 (3.0)
	Urine Protein		≥1	71	11 (15.5)	143	13 (9.1)	141	20 (14.2)
	Urobilinogen		≥1	60	6 (10.0)	143	8 (5.6)	129	6 (4.7)

Safety in special populations

Intrinsic Factors

Population PK Analyses of Tafamidis in Healthy Volunteers, Patients with Hepatic Impairment, and Patients with Transthyretin Amyloidosis

In order to examine the effect of certain intrinsic factors including age, gender, race, health status, and renal function on the PK of tafamidis, a population PK analysis was conducted (Module 5.3.3.5 Report PMAR-EQDD-B346a-Other-452). Results from this analysis showed that no dosage adjustment is necessary with tafamidis for intrinsic or extrinsic factors, including gender, race, age, nor for subjects

with renal impairment or mild and moderate hepatic impairment. No data are available in patients with severe hepatic impairment. The results from these studies support tafamidis once-daily oral dosing.

Patients with ATTR-CM were older (mean of 74.7 years versus 34.8 or 44.5 years in healthy volunteers and patients with ATTR-PN, respectively) and had a lower baseline creatinine clearance (mean of 56.4 mL/min versus 123.7 or 101.7 mL/min in healthy volunteers and patients with ATTR-PN, respectively) than healthy volunteers or patients with ATTR-PN. Patients with ATTR-PN also tended to have a smaller body weight than other populations (mean of 65.1 kg versus 76.1 or 80.1 kg in healthy volunteers and patients with ATTR-CM, respectively). The distribution of other continuous covariates was relatively similar among different populations.

Based on the population PK analyses, subjects ≥65 years had an average 15% lower estimate of tafamidis clearance at steady state compared to subjects < 65 years. This difference in clearance results in <20% increases in mean Cmax and AUC compared to younger subjects and is not clinically significant. Therefore, no dosage adjustment is necessary in subjects ≥65 years.

In Study B3461028, patients with Baseline NYHA Class IV were excluded.

Based on these analyses, the large nonclinical safety margins, and the tolerability profile as demonstrated in the clinical studies, no dose adjustment is recommended for any intrinsic or extrinsic factor.

In ATTR-CM patients, the impact of age, race, gender, TTR genotype, baseline NYHA classification, and geographic region on incidence of TEAEs (all-causality and treatment-related), SAEs, AEs leading to discontinuation, and deaths was evaluated. The review of key safety data from the B3461028 Cohort revealed a potential subset, although small, of ATTR-CM patients who might have higher risk for certain events. Patients identified at baseline as NYHA Class III demonstrated higher rates of AEs, SAEs, and AEs and SAEs leading to discontinuations, and deaths than those patients identified at baseline as NYHA Class I/II. These elevations in exposure-adjusted incidence rates were apparent in the placebo and tafamidis treatment groups; however in each case, the incidence of the key safety event was numerically lower for tafamidis-treated patients than for placebo-treated patients. With regard to discontinuations from study, the reason for discontinuation with the largest increase in the NYHA Class III versus NYHA Class I/II was deaths, for placebo and tafamidis treatment groups. See Module 5.3.5.3 B3461028 Cohort Safety Table 2.2.6.a.

Extrinsic Factors

There was no assessment of the effects of extrinsic factors such as tobacco or alcohol use on the safety of tafamidis. As noted in Module 2.7.2.3.3.6, the effect of food on absorption was minimal and is not expected to impact the safety of tafamidis.

Use in Pregnancy and Lactation

Female patients who were pregnant or lactating were excluded from all clinical trials in the development program of tafamidis. There are no adequate data on the use of tafamidis in pregnant women. Studies in animals have shown reproductive toxicity (Module 2.4.4.6). There was no evidence of adverse effects of tafamidis on fertility or reproductive performance in the rat (Module 2.4.4.6.1). In a developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, reduced embryo/foetal survival, and reduction in foetal weights were observed at or below the human equivalent dose (HED) (Module 2.4.4.6.3). Post-natal mortality and developmental anomalies were observed in rats at dose levels ≥14x, ≥3.4x and ≥2.8x the doses of 20 mg tafamidis meglumine, 80 mg tafamidis meglumine, and 61 mg tafamidis, respectively. However, the potential risk for humans is unknown. Tafamidis should not be administered to pregnant women or women planning to become

pregnant. Contraceptive measures should be used by women of childbearing potential during treatment with tafamidis and, given the long half-life of tafamidis, for 1 month after stopping treatment.

The effect of tafamidis on nursing infants after administration to the mother has not been studied. However, animal data demonstrate that tafamidis is secreted in the milk of lactating rats (Module 2.4.3.6). Therefore, lactating women should not receive treatment with tafamidis. No information is available on the presence of tafamidis in human breast milk.

As of 15 June 2018, there were 22 cases of exposure in utero to tafamidis during or within 1 month prior to pregnancy in the overall tafamidis program (clinical and non-interventional studies). Of these 22 cases, 12 were described as maternal exposure during pregnancy, 10 were exposure via father. The pregnancy outcomes of these 22 cases (includes 24 foetuses) were: 14 normal newborns (including 1 low birth weight and 2 pre-term infant), 5 unknown outcomes, 2 spontaneous abortions, 1 medical termination (twins), and 1 voluntary abortion. In one case, intense vaginal haemorrhage occurred during 1st trimester in 31-year-old patient expecting twins. Upon discovery of pregnancy, tafamidis was stopped during 11th week of gestation; however, vaginal bleeding continued and patient underwent a medical termination of pregnancy as a consequence of intense vaginal bleeding. No further reports of tafamidis exposure during pregnancy have been received spontaneously within the post-marketing experience.

The Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) program follows the progress and outcome of reported pregnancies in women exposed to tafamidis. The objective of TESPO is to evaluate outcomes of pregnancy (including major birth defects and/or developmental abnormalities in live born children) in patients with ATTR-PN with exposure to tafamidis during or within 1 month prior to pregnancy. This surveillance is undertaken to further monitor the important potential risk of reproductive toxicity for tafamidis arising from findings in animal developmental toxicity studies (Module 2.4.4.6; Module 2.4.4.6.4). Of the 14 normal newborns born to mothers directly and indirectly (through their partner) exposed to tafamidis, 7 had post-natal follow-up at 1 year. All 7 infants survived the first year of life and have met their age-appropriate development milestones. No infant had any congenital malformations.

Overdose

In clinical studies of ATTR-CM patients, the highest daily dose provided was tafamidis 80 mg, with the longest duration of exposure being 111 months. Two patients in Study B3461045 experienced an acute overdose during clinical trials. Both involved the accidental ingestion of a single tafamidis dose of 160 mg without the occurrence of any associated adverse events (Module 5.3.5.3 All Tafamidis Cohort Listing 16.9.1). The highest dose of tafamidis given to healthy volunteers in a clinical trial was 480 mg in a single dose. There was one reported treatment-related adverse event of mild hordeolum at this dose. (Module 5.3.3.1 Study B3461040 Report Body).

Dogs were administered tafamidis (in 0.5% methylcellulose) at single doses up to 600 mg/kg (333 mg/kg HED) via oral gavage without apparent adverse effects. This dose level was approximately 1904x, 476x, and 382x the clinical doses of 20 mg tafamidis meglumine, 80 mg tafamidis meglumine, and 61 mg tafamidis, respectively. Thus, the risk for inadvertent or intentional overdose in humans is considered to be low.

Drug Abuse

There is no evidence that tafamidis has dependence potential. No drug abuse of this medication has been observed or is anticipated based on the pharmacology and receptor binding.

Withdrawal and Rebound

No effects of withdrawal and rebound of this medication have been observed. There were no adverse effects noted in patients who abruptly terminated treatment with tafamidis (e.g., patients who went to

liver transplant were required to discontinue treatment with tafamidis prior to transplant). This medication is intended for long-term use.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects of tafamidis on the ability to drive or use machines have been performed; however, there have been no adverse reactions identified that would be expected to affect the ability of a patient to drive or operate machinery.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

- Tafamidis is not expected to significantly induce or inhibit cytochrome (CYP) P450 enzymes or inhibit uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes at clinically relevant concentrations.
- Tafamidis showed a low potential to inhibit MDR1 (P-gp) (systemically), organic cation transporter (OCT), OCT2, multidrug and toxin exclusion transporter (MATE), MATE1 and MATE2K, organic anion transporting polypeptide (OATP), OATP1B1, and OATP1B3 at clinically relevant concentrations.
- Tafamidis meglumine inhibits the uptake transporters OAT1 and OAT3 (organic anion transporters) and may cause drug-drug interactions at clinically relevant concentrations with substrates of these transporters (e.g. non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine) following 20 mg or 80 mg.
- Tafamidis has the potential to inhibit breast cancer resistant protein (BCRP) (systemically and in the GI tract) and may increase exposure of substrates of this transporter (eg, methotrexate, rosuvastatin, imatinib) following 20 mg or 80 mg tafamidis meglumine administration.

Discontinuation due to adverse events

Discontinuation from study treatment due to TEAEs

Patients experiencing TEAEs leading to permanent discontinuation of treatment occurred more frequently in the placebo group (28.8%) than in the tafamidis 20 mg group (18.2%) and tafamidis 80 mg group (22.7%) (Module 5.3.5.3 B3461028 Cohort Safety Table 4.1.1.a).

For the B3461028 Cohort, the SOC most commonly associated with discontinuations from study treatment was cardiac disorders, with 25 (14.1%) in placebo, 10 (11.4%) in tafamidis 20 mg, 20 (11.4%) in tafamidis 80 mg, and 30 (11.4%) in the pooled tafamidis group. The most frequently reported adverse events leading to discontinuation in any treatment group were cardiac failure, congestive cardiac failure, cardiac amyloidosis and disease progression.

For the B3461028 Cohort, permanent discontinuation of study treatment due to SAEs occurred more frequently in the placebo group (28.2%) compared to any tafamidis group; 17%, 22.2%, and 20.5% in the tafamidis 20 mg, 80 mg and pooled tafamidis, respectively. The most common SOC for SAEs leading to study treatment discontinuations were cardiac disorders, with percentages in the placebo, tafamidis 20 mg, and tafamidis 80 mg treatment groups of 14.1%, 10.2%, and 11.4%, respectively. The most frequent SAEs associated with study treatment discontinuation were similar to those for TEAEs as noted above.

Interruptions and dose reduction due to adverse events

For the B3461028 Cohort, requests for dose reductions due to adverse events were infrequent, and occurred more often in the placebo group (4 patients) than in the tafamidis group (2 patients, tafamidis 80 mg). Actual dose reductions to 40 mg daily due to adverse events occurred in 2 patients in the tafamidis 80 mg group (0.8% of tafamidis-treated patients overall) (Module 5.3.5.3 B3461028 Cohort Safety Table 13.3.a) and were for AEs of moderate urinary tract pain and moderate headache, occurring 15 and 113 days after first dose of blinded study medication, respectively (S0115 Module 5.3.5.3 Study B3461028 Report Body Table 14.3.1.1.3.1).The urinary tract pain resolved 4 days after dose reduction, and the patient continued treatment with tafamidis 40 mg into Study B3461045. The event of headache resolved 3 days after dose reduction, and 3 months later the patient withdrew from the study, per protocol guidelines, due to a heart and kidney transplant.

Post marketing experience

Table 23: Most Frequently (n > 4) Reported PTs of Spontaneous Reports in Safety Database in ATTR-PN Patients

Preferred Term	Non-serious	Serious	Total
Disease progression	14	14	28
Diarrhoea	15	7	22
Hereditary neuropathic amyloidosis	8	8	16
Drug ineffective	15	-	15
Vomiting	9	6	15
Condition aggravated	6	8	14
Urinary tract infection	4	6	10
Cardiac failure	-	9	9
Malaise	8	1	9
Therapy non-responder	8	-	8
Death	-	7	7
Abdominal pain	3	3	6
Asthenia	5	1	6
Fall	1	5	6
Nausea	3	3	6
Anal incontinence	1	4	5
General physical health deterioration	2	3	5
Haematuria	2	3	5
Paraesthesia	5	-	5
Product use in unapproved indication	5	-	5
Product use issue	5	-	5
Pyrexia	1	4	5

Source: Pfizer safety database.
Cut-off date of 15 June 2018.
Adverse events coded using MedDRA version 21.0.
Abbreviations: PT = preferred term.

2.6.1. Discussion on clinical safety

The safety profile of tafamidis for the treatment of ATTR-CM has been evaluated from the completed pivotal Phase 3 Study B3461028. In addition, data from the ongoing long-term extension (LTE) Study B3461045, as well as the completed Phase 2 Study B3461025 and associated ongoing LTE, Study B3461026 are included. Data provided for both ongoing LTEs utilized a cut-off date of 15 Feb 2018.

Additional supportive data from ATTR-PN patients in clinical trials and from post-marketing experience in ATTR-PN patients (cut-off date 15 June 2018) are also included, as well as further supportive safety data from tafamidis-treated patients enrolled in Study B3461001 (Transthyretin-Associated Amyloidosis Outcomes Survey [THAOS]; cut-off date 15 February 2018).

As general comment, the presentation of the scattered data in different modules made the analysis difficult. The provided supplied computer links did not allow to retrieve easily the complete information regarding the extension request.

On the other hand, the MAH provided data associating results of studies from line extension in ATTR-CM and those resulting from the indication in ATTR-PN. Supplemental data for phase I studies were not presented separately.

Furthermore, regarding studies in ATTR-CM, the MAH mostly analysed safety data by comparing placebo to pooled Tafamidis 20mg and 80mg together and did not compare the two dosages 20mg and 80mg between them. This does not allow to compare the safety profiles according to the dose.

There were no differences in demographic characteristics between patients groups and study B3461028, Broad cohort and all tafamidis cohort. In study B3461028, regarding ethnicity data, the MAH divided the patients between "Hispanic or latino" and "not Hispanic or latino". ATTR-CM, known as familial amyloid cardiomyopathy, is associated with genetic variants of TTR such as Val122Ile and Leu111Met. The variant TTR genotype (Val122Ile TTR) occurs in 3,3% to 4% of the US African-American population and is exceedingly rare in White patients.

Variant TTR genotype was well balanced between the two treatments arm tafamidis 20mg and 80mg: about 24% of patients in each group in the pivotal study B3461028, and 21% in the Broad study. However, in the Broad Study, "Hispanic or latino" patients were slightly higher in the tafamidis 20mg arm compared to the tafamidis 80mg arm (3,5% vs 1,8%).

The company explained why "Hispanic or latino" ethnic group has been separated from the other patients. The classification categories of ethnicity (Hispanic or Latino OR not Hispanic or Latino) recommended in the guidance are social-political constructs and should not be interpreted as being scientific or anthropological in nature. These ethnicity categorisation subgroups were not used for analysis purposes.

Overall, results from the pivotal Phase 3 Study B3461028 demonstrate that oral tafamidis meglumine-dosed at either 20 mg or 80 mg once daily was well tolerated with a safety profile comparable to placebo when used for the treatment of adult patients with ATTR-CM due to either variant or wild-type TTR. The majority of events were mild to moderate in severity. Severe related adverse events were slightly reported compared to mild or moderate related TEAEs in all treatment groups.

A smaller proportion of patients discontinued due to adverse events in the tafamidis-treated groups compared to placebo. Distribution of TEAEs (non-serious and serious) was generally similar among placebo and tafamidis-treated patients. Overall, no new major safety concerns were identified in patients with ATTR-CM treated with tafamidis as compared to the safety profile identified in ATTR-PN patients.

If comparison between placebo and tafamidis treatment does not show any major discrepancies, the comparison between tafamidis 20mg and tafamidis 80mg revealed interesting differences.

Some adverse events were reported more frequently with tafamidis 80mg compared to tafamidis 20mg: Diarrhea and nausea were reported more often in patients treated with tafamidis 80mg compared to tafamidis 20mg: 8% vs 2,3% for diarrhea and 5,7% vs 1,1% for nausea. As well for "Pain in extremity" more reported with tafamidis 80mg (15,3%) compared with tafamidis 20mg (6,8%).

At the opposite, UTI was more frequently reported with tafamidis 20mg than with tafamidis 80mg (5,7% vs 2,3%).

Regarding AEs reported in the "Cardiac disorders" SOCs, "cardiac failure acute" was more reported in patients treated with tafamidis 80mg (13,6%) compared to patients treated with 20mg (4,5%).

Cardiac failure acute in patients treated with tafamidis 80mg remained higher through all treatment periods compared to patients treated with tafamidis 20mg. Frequencies of cardiac failure acute reported with tafamidis 80mg was similar to those reported with placebo (see table summarizing number of subjects treated by period and by arm and number of subjects with acute cardiac failure).

The MAH discussed why "cardiac failure acute" are more reported in the tafamidis 80mg treatment arm compared to tafamidis 20mg. Due to the fact that verbatim terms utilized by different investigators may vary when describing similar adverse events, heart failure may be coded as "cardiac failure" or "cardiac failure acute" when MedDRA coding is programmatically applied at the Preferred Term (PT) level. That's why the MAH reviewed all relevant PTs in the "Cardiac Failure" Standardised MedDRA Query (SMQ) [Narrow]. The data presented do not differentiate doses of 20mg and 80mg or placebo in terms of TEAEs that are quite comparable. The discrepancy for acute cardiac failure probably stems from the fact that the term Narrow « Cardiac Failure acute » fluctuates between the groups but is compensated for by other "narrow" terms equally valid for defining acute heart failure. When all the "narrow" terms are cumulated there is no difference. Moreover, list of TEAEs by MedDRA SOC and PT (Table 14.3.1.2.3.3.1) do not show any difference between the 2 tafamidis dosages regarding SOC Cardiac disorders (60.2%, 55.1% and 61.6% of TEAEs reported respectively in tafamidis 20mg, tafamidis 80mg and placebo group). Therefore question related to pharmacological reason no longer seems to be justified.

Concerning cases with fatal outcome included in study B3461028, 144 cases of death were retrieved during the study. 94/144 were reported to disease under study. 50 cases were reported from other ethiology (42 other and 8 unknown). This represents 6 patients (6,8%) with tafamidis 20mg, 21 patients (12%) with tafamidis 80mg and 23 patients (13%) with placebo. Number of deaths not due to disease progression was slightly higher in the tafamidis 80mg arm compared to the 20mg arm.

The MAH discussed the 50 death cases not due to disease progression in study B3461028. Cases related to pneumonia, septic shocks or cardiac failure were all assessed as unrelated to study drug.

Regarding dose reduction due to adverse events, two subjects included in the tafamidis 80mg treatment group presented dose reduction due to related adverse events (moderate urinary tract pain and moderate headache).

The possibility of dose reduction in case of adverse events may be a problem with the choice of a single high dose (61mg). The MAH suggests that because there are only 2 cases of dose-reduction and that the safety profile of the tafamidis 80mg group was comparable to the placebo or tafamidis 20mg groups, the need for a dose reduction is not warranted. Even if the safety profile of tafamidis 80mg appears to be well tolerated, there are no safety data available with tafamidis 61mg in phase 3 clinical trials. In the phase 1 clinical trials (B3461054 and B3461056), "headache" is described as the most reported TEAEs. The few cases concerning dose reduction with tafamidis 80mg does not allow to state that there will be no safety problem with the 61mg dosage.

Laboratories abnormalities and their potential clinical impact.

Low neutrophils count was the abnormal laboratory values often reported in the tafamidis group in healthy subjects (8 HV patients (2,7%) vs 1 (1,4%) in placebo group). In the B3461028 pivotal study, low neutrophils count was also more often observed with tafamidis (80mg and 20mg) compared to placebo: Neutrophils <0.8 x LLN 1,9% with tafamidis 80mg, 1,2% with tafamidis 20mg and 0,6% with placebo. It is to be noted that pneumonia were mostly reported in patients treated with tafamidis (pooled data 20mg and 80mg) compared to the placebo (12,25% vs 9,5%). Moreover 6 cases of pneumonia and 6 cases of septic shock were reported in the line-listing of deaths for study B3461028.

In the last PSUSA 00002842/201805 20 of the 25 septic cases issued from clinical trials concerned studies performed in ATTR-CM patients.

The MAH discussed the risk of sepsis or infections in the ATTR-CM patients treated with tafamidis, taking into account the biological results observed for neutrophils count. The incidence for sepsis and sepsis-related TEAEs, as for serious TEAEs, in study B3461028 are comparable among the treatment groups. Provided safety data did not highlight a relationship between tafamidis and infections and dose-related effect. Regarding evolution of neutrophil counts during study B3461028, changes from Baseline by visit up to 30 months shows no evidence of sustained decrease in neutrophil counts for both tafamidis groups compared to placebo group. Moreover, as discussed in Question 84, death cases related to pneumonia and septic shocks were all assessed as unrelated to study drug. The provided data are reassuring.

Regarding treatment related hepatic events (table 49), "liver function test increased" was mostly reported with tafamidis 80mg compared to placebo and tafamidis 20mg (3,4% vs 0,6% vs 0% respectively). Gamma-glutamyltransferase was more reported with tafamidis (3,4%with tafamidis 80mg and 2,3% with tafamidis 20mg) compared to placebo (2,8%).

Among the 19 hepatic events possibly related to tafamidis, 15 concerned patients treated with tafamidis 80mg (only 4 patients on tafamidis 20mg). The two reported case of dose interruption (10011004, 10011004) due to increase of liver function concerned patients treated with tafamidis 80mg. Dose was not changed in 17 cases; Cases resolved without dose change in 9 cases. Although the 19 reported cases did not raise significant hepatic risk, the cases were mostly reported with tafamidis 80mg.

To be noted in non-clinical studies, Tafamidis-associated hepatic alterations were observed at exposures approximately ≥0.7-times the human exposure at a dose of 61 mg tafamidis and 2.5-times the human exposure at a dose of 20 mg tafamidis meglumine.

Hepatotoxicity is an important potential risk mentioned in the risk management plan (RMP) of Vyndaqel 20 mg.

Given these data, although biological results and clinical data did not raise significant risk of hepatic damage, hepatotoxicity should continue to be closely monitor with tafamidis, especially with the high dosage.

Due to the high affinity binding of tafamidis to the thyroxine receptor, there is a theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer.

In the B3461028 Cohort, a decrease from baseline in mean total thyroxine values was observed in both the tafamidis 20 mg and tafamidis 80 mg groups with greater decrease in tafamidis 80 mg: Thyroxine <0,8x LLN 29,9% with tafamidis 80mg, 12,3% with tafamidis 20mg and 4,5% with placebo.

Treatment-related thyroid-related TEAEs by patient in all tafamidis cohort were reported: 8 cases were reported; one case of hyperthtyroidism and 7 cases of hypothyroidism. Among the 7 cases of hypothyroidism, 5 concerned tafamidis 80mg. Changes in thyroid dysfunction are an important potential risk in the RMP of Vyndaqel 20mg.

Although biological results and clinical data did not raise significant risk of thyroid damage, changes in thyroid function should continue to be closely monitored with tafamidis, especially with the high dose as reflected in the agreed RMP.

Assessment of paediatric data on clinical safety

N/A

2.6.2. Conclusions on the clinical safety

The safety profile of tafamidis for the treatment of ATTR-CM did not reveal any major safety concern. Results from the pivotal Phase 3 Study B3461028 demonstrate that oral tafamidis meglumine-dosed at either 20 mg or 80 mg once daily was generally well tolerated with a safety profile comparable to placebo. The majority of events were mild to moderate in severity.

However, even if the safety profile of tafamidis 80mg appears to be well tolerated, it should be kept in mind that there are no safety data available with tafamidis 61mg in phase 3 clinical trials. The few cases concerning dose reduction with tafamidis 80mg do not allow to state that there will be no safety problem with the 61mg dosage**.**

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risk	None
Important potential risk	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

Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study B3461029 (Fx-R-001-S2) A THAOS substudy evaluating the effects of tafamidis on disease progression in patients with non-Val30Met mutations and symptomatic neuropathy On-going	Quantify disease progression in the target population via at least a 12-month standard of care period. Evaluate the effects of 12 months of tafamidis therapy on disease progression following the 12-month standard of care period. Compare rates of disease progression before and after the initiation of treatment with tafamidis. Evaluate the safety of tafamidis in the study population.	Important potential risks – Hepatotoxicity; Changes in thyroid function, particularly in pregnant women; Reproductive and developmental toxicity and lactation. Missing information –, ATTR NYHA Class IV, Safety and efficacy in patients with ATTR-PN mutations other than Val30Met and severe hepatic impairment.	Final Report	15 May 2022
Category 3 - Required additional pharmacovigilance activities				
B3461001 (Fx-R-001) Transthyretin Amyloidosis Outcomes Survey (THAOS) registry Global, multicentre, longitudinal, observational survey of patients with documented	For tafamidis-treated participants, collect and summarise all AE and SAE data, including for the specific safety concerns outlined as identified and potential risks, and	Important potential risks – Hepatotoxicity; Changes in thyroid function, particularly in pregnant women. Missing information –, ATTR NYHA Class IV, Safety and efficacy in	End of study Final Report	16 June 2023 16 May 2024

transthyretin (TTR) mutations or wild-type TTR amyloidosis On-going	missing information. For all THAOS participants (tafamidis-treated and those not treated with tafamidis due to choice, lack of access, or a diagnosis inconsistent with the labelled indication for tafamidis), collect and summarise additional data on the events of interest listed above, as applicable. *Other study objectives as follows:* To describe the population of patients affected with TTR-associated amyloidosis (ATTR), including hereditary ATTR and wild-type ATTR. To enhance the understanding of disease natural history, including the variability and progression of the hereditary and acquired forms of the disease. To better understand the genotype – phenotype	patients with ATTR-PN mutations other than Val30Met and severe hepatic impairment.		

	relationship in hereditary ATTR. To foster an international community of medical experts who will develop recommendations on the clinical management of ATTR. To better understand, manage and treat patients with ATTR through publication of the survey data.			
B3461042 Post-marketing safety surveillance study in Japanese patients with ATTR-PN On-going	Long-term safety and efficacy in Japanese subjects	Important potential risks – Hepatotoxicity; Changes in thyroid function, particularly in pregnant women; Reproductive and developmental toxicity and lactation. Missing information – NYHA Class IV patients, Safety and efficacy in patients with ATTR-PN mutations other than Val30Met and severe hepatic impairment.	Final report	July 2023
Tafamidis enhanced surveillance pregnancy	The TESPO program is intended to improve data collection on pregnancy	Important Potential risk- Reproductive and developmental	On-going	None planned unless indicated by data, updated information on the topic will be included in

outcomes (TESPO) On-going	outcomes in this limited population of patients who receive tafamidis during pregnancy	toxicity and lactation.		periodic safety reports

Risk minimisation measures

Safety concern	Risk Minimisation Measures
Important potential risks	
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None.
Changes in thyroid function, particularly in pregnant women	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction Additional risk minimisation measures: None.
Reproductive and developmental toxicity and lactation	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC section 4.6 Fertility, pregnancy and lactation. Additional risk minimisation measures: HCP Guide
Missing information	
Patients with NYHA Class IV (ATTR-CM indication)	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Additional risk minimisation measures: HCP Guide
Patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Section 5.2: Pharmacokinetic properties Additional risk minimisation measures: None.

Safety and efficacy in patients with ATTR-PN mutations other than Val30Met	Routine risk minimisation measures: Vyndaqel 20 mg SmPC Sections: 5.1, Pharmacodynamic properties Additional risk minimisation measures: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vyndaqel (tafamidis) is included in the additional monitoring list as the Marketing Authorisation is granted under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication is for the treatment wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

The disease, also called ATTR-CM in this document, is caused by the accumulation of misfolded transthyretin (TTR) amyloid fibrils in the myocardium, leading to restrictive cardiomyopathy, heart failure, and ultimately in death.

The aim of new treatment is to reduce all-cause mortality and cardiovascular-related hospitalisation.

3.1.2. Available therapies and unmet medical need

There are currently no approved pharmacologic treatments for ATTR-CM.

All drugs authorized to treat patients with hereditary TTR amyloidosis are only indicated in patients with symptoms of polyneuropathy (ATTR-PN): tafamidis 20mg (VYNDAQEL), inotersen (TEGSEDI), patisiran (ONPATTRO).

Treatments to manage ATTR-CM symptoms include a broad range of medications used to treat heart failure, pacemaker placement for cardiac arrhythmias. Liver and/or heart transplantation may be an option for some patients (Falk 2011).

Hereditary ATTR-CM, inherited by a mutation in the TTR gene, appears aggressive with a median survival of about 26 months. Wild-type ATTR-CM is a more progressive disease, caused by the deterioration of TTR with age, with a median survival of about 43 months (Ruberg et al. 2012).

It can be concluded that there is a significant unmet medical need in both hereditary and wild-type ATTR-CM patients for an effective and safe treatment to slow the progression of disease and improve patient outcomes.

Of note, early access demands of Vyndaqel 20mg to treat ATTR-CM patients are handled at national levels in some of the Member States.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase 3, multicenter, randomised, double-blind, 3-arm, placebo-controlled study comparing 2 arms with tafamidis (20mg dose arm and 80mg dose arm) versus placebo in 441 hereditary and wild-type ATTR-CM patients with a 30-month duration of double-blind treatment.

3.2. Favourable effects

Favourable effects of tafamidis pooled 20mg and 80mg:

According to the primary analysis performed with the Finkelstein-Schoenfeld method, treatment with tafamidis (pooled 20mg and 80mg arms) was superior to placebo over 30 months ($p<0.001$).

Regarding the components of the Finkelstein-Schoenfeld analysis:

- all-cause mortality at month 30 was reduced by 30.2% in the tafamidis groups compared to placebo: 29.5% with pooled tafamidis vs 42.9% with placebo, statistically significant (p=0.0259), with a difference between groups observed after 16 months of treatment.

- the frequency of CV-related hospitalizations per year for the ITT analysis set was reduced by 32.3% with pooled tafamidis compared to placebo: 52.3% with tafamidis vs 60.5% with placebo, statistically significant (p<0.0001).

The win ratio for the primary analysis is 1.695 (95% CI 1.255, 2.289), indicating that a tafamidis-treated patient had a 69.5% higher chance of having a better outcome based on a hierarchical combination of all-cause mortality and CV-related hospitalisation relative to a placebo patient.

Regarding key secondary endpoints, tafamidis reduced, at month 30, the decline in the distance walked during the 6-minute test as compared with placebo (difference of 75.68 metres [SE, ±9.24; p<0.001]) and in the KCCQ-OS score as compared with placebo (difference of 13.65 points [SE, ±2.13; p<0.001]).

The same trend as the primary endpoint was observed for CV-related mortality, which was a secondary endpoint, with a reduction by 30.9% in the tafamidis groups compared to placebo: 20.1% with pooled tafamidis vs 28.2% with placebo, (p=0.0383), and a difference between groups observed after 16 months of treatment.

Regarding the secondary endpoint TTR stabilisation at Month 1, significantly more patients in the pooled tafamidis group (86.1%) demonstrated TTR stabilisation than was observed for patients in the placebo group (3.5%), (p<0.0001).

Regarding subgroup analyses, the following favourable results are of interest:

- Regarding TTR genotype, results were consistent for both hereditary and wild-type ATTR-CM, with favorable results observed with tafamidis compared to placebo, for the Finkelstein-Schoenfeld primary analysis on all-cause mortality and CV-related hospitalizations, its components, the distance walked during the 6-minute test and the KCCQ-OS score, CV-related mortality and TTR stabilization at Month 1.

- Regarding NYHA Class I-II, favorable results were observed with tafamidis compared to placebo for the Finkelstein-Schoenfeld primary analysis on all-cause mortality and CV-related hospitalizations, its components, the distance walked during the 6-minute test and the KCCQ-OS score, CV-related mortality and TTR stabilization at Month 1.

- Regarding NYHA Class III, favorable results were observed with tafamidis compared to placebo for all-cause mortality only in the composite primary endpoint, and key secondary endpoints at Month 30 (distance walked during the 6-minute test and the KCCQ-OS score).

Favourable effects of separate doses (tafamidis 20 mg or tafamidis 80 mg):

The study was not powered to conclude on a difference between doses. In fact, the observed results do not allow at all to distinguish better favourable effects of the 80mg over the 20mg dose on any clinical endpoints. Even, there was a trend to slightly reduced events in the 20mg compared to the 80mg on the main clinical efficacy endpoints.

- Both separate 20 mg and 80 mg doses of tafamidis were superior to placebo over 30 months on the Finkelstein-Schoenfeld primary analysis of all-cause mortality and frequency of CV-related

hospitalisations: p=0.0048 with the 20 mg and p=0.0030 with the 80 mg group. This is confirmed when focusing on the win-ratio of both doses, respectively 1.81 and 1.64 for the 20 mg and 80 mg.

The same favorable results were observed with both separate 20 mg and 80 mg doses for both of the components of the primary analysis (all-cause mortality and CV-related hospitalizations, key secondary endpoints at Month 30 (distance walked during the 6-minute test and the KCCQ-OS score), other secondary endpoints (CV-related mortality, TTR stabilization at Month 1), exploratory endpoints (NT-proBNP and troponin I).

- Separate dose of 80mg: A higher favourable effect of the 80mg compared to the 20mg was only presented on the post hoc exploratory endpoints on the reduction of NT-proBNP and troponin I at Month 30 (p=0.0468 and p=0.2479).

- Separate dose of 20mg: A trend to a higher favourable effect of the 20mg compared to the 80mg was observed with lower events in the 20mg dose group compared to the 80mg dose group on all the clinical endpoints: all-cause deaths (27.3% with the 20mg vs 30.7% with the 80mg), CV-related hospitalization (47.7% with the 20mg vs 54.5% with the 80mg) and also CV-related deaths (21.6% with the 20mg vs 25.6% with the 80mg).

3.3. Uncertainties and limitations about favourable effects

- Patients without symptoms of heart failure - NYHA Class I: a medical need and a clinical benefit cannot be clearly drawn from clinical pivotal results, considering the weak number of included NYHA Class I patients (<10%)

There are some uncertainties regarding patients with NYHA Class I. Indeed, the diagnosis ATTR-CM cannot be formally established without a number of specific procedures (biopsy, scintigraphy, TTR identification, genotyping…). Such heavy clinical management could be questionable in patients without symptoms of heart failure, while a clinical benefit can be considered as expected, despite the weak number of included NYHA Class I patients in clinical pivotal study (<10%). There is a risk of misuse in the elderly in the absence of clear diagnosis of ATTR-CM. A genotyping test in a family context is not the only reason to diagnose ATTR-CM in NYHA Class I patients.

- Patients with NYHA class III: unlikely to benefit

In patients with NYHA class III, the rates of CV-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (76.9% vs 58.7%) and CV-related mortality tended to be higher with tafamidis compared to placebo (51.3% vs 49.2%).

Further analyses according to the doses and time course have been provided to better characterise the effect of tafamidis, notably in more severe patients who may not benefit from this treatment.

Regarding when does tafamidis shows evidence of effect, it is clear from the 6MWT and the KCCQ OS Ls means that it does start to effect early: as early as 6 months, which is very relevant in this population with untreated short survival. Unlike expected, there was no evidence that the higher dose had a distinct effect on clinical response, even when the biological biomarkers of MoA (tafamidis stabilisation) and disease severity (NTproBNP) detach also early.

As from above, there is unfortunately no clinical evidence that treating with a higher dose starts working earlier, or that the benefit is sure at 30 months time. The biomarker data cannot be a sufficiently robust assurance of better effect.

- Choice of the 80mg dose rather than 20mg

The data presented to distinguish a pharmacological benefit between 80mg and 20 mg were not considered relevant. The post hoc exploratory endpoints NT-proBNP and troponin I were not endorsed from methodological and clinical points of view.

The Applicant argumentation based on a differentiation between the doses on the all-cause mortality analysis from B3461045 data (reduction in risk of death for patients on the tafamidis 80 mg dose relative to 20 mg) was not endorsed from a methodological point of view. However, data regarding group analysis of the re-randomised placebo arm to 20 mg or 80 mg of tafamidis have been provided. Further sensitivity analysis, considering relevant co-factors such as NYHA class, age, NT-proBNP and mortality have also been performed.

From the provided results, it can be admitted that in the studied population as a group, the 80 mg dose may seem a bit more effective than the 20 mg dose. Still, the imbalances in the re-randomized population cannot allow an absolute certitude. Analysis favoured 80 mg dose; but even when adjusted for age, NT-proBNP, and 6MWT did not have the 95CI detached from 1.0.

A trend of a higher favourable effect of the 20mg compared to the 80mg was observed with lower events in the 20mg dose group compared to the 80mg dose group on all the clinical endpoints: all-cause deaths (27.3% with the 20mg vs 30.7% with the 80mg), CV-related hospitalization (47.7% with the 20mg vs 54.5% with the 80mg), confirmed when focusing on the win-ratio of both doses (1.81 for the 20 mg and 1.64 for the 80 mg), and also CV-related deaths (21.6% with the 20mg vs 25.6% with the 80mg). However the Applicant chose not to apply for the cardiology indication for the 20mg.

TTR % stabilisation values

estimated in the pharmacological program for the 80mg dose selection were questionable, since results from the phase III pivotal study reveal comparable rates at 12 months between the 2 doses arms: 82.7% with the 20mg and 87.8% with the 80mg. This was disturbing since the study was more powered for the 80mg group, with twice more patients than in the 20mg group and the dose of 80mg was 4 time higher than the 20mg.

- New formulation of 61 mg tafamidis free acid: bioequivalence to 4 x 20 mg formulation

This formulation has been studied only in short term PK/PD studies and failed to formally prove bioequivalence with the 4x20 mg formulation on single dose study in accordance to guidelines. Efficacy and safety data from clinical study in the target population with the 61mg formulation are lacking.

However, considering the reassuring safety data and the efficacy benefits in a large range of daily doses (20mg and 80mg), the approval of the 61mg formulation was agreed in this particular case, despite the above mentioned limits.

The applicant justified why steady state conditions are the most relevant here. They acknowledged that formal bioequivalence has not been proven, but in the context, changes in exposure, and higher Cmax in particular, are not expected to be relevant.

3.4. Unfavourable effects

Regarding safety, overall, the results from the pivotal Phase 3 Study B3461028 demonstrate that oral tafamidis meglumine dosed at 80 mg once daily was well tolerated with a safety profile comparable to placebo when used for the treatment of adult patients with ATTR-CM due to either variant or wild-type TTR. The majority of events were mild to moderate in severity. Severe related adverse events were slightly reported compared to mild or moderate related TEAEs in all treatment groups. A smaller proportion of patients discontinued due to adverse events in the tafamidis-treated groups compared to

placebo. Overall, no major safety concerns were identified in patients with ATTR-CM treated with tafamidis as compared to the safety profile identified in ATTR-PN patients.

- Patients with NYHA class III: unlikely to benefit

In patients with NYHA class III, the rates of CV-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (76.9% vs 58.7%) and CV-related mortality tended to be higher with tafamidis compared to placebo (51.3% vs 49.2%).

In this context, the decision to start or maintain treatment should be taken at the discretion of the cardiologist, as mentioned in section 4.2 of the SPC.

- Safety of pooled tafamidis:

Treatment emergent adverse events (TEAs) "asthenia" and "pneumonia" were mostly reported in patients treated with tafamidis (pooled data 20mg and 80mg) compared to the placebo: 11,3% vs 6,2% for asthenia and 12,25% vs 9,6% for pneumonia.

Low neutrophils count (<0.8 x LLN) was the abnormal laboratory values reported more in the tafamidis group compared to placebo: 1,9% with tafamidis 80mg, 1,2% with tafamidis 20mg and 0,6% with placebo.

- Safety of 80mg tafamidis:

Some adverse events were more reported with tafamidis 80mg compared to tafamidis 20mg: diarrhea and nausea (8% vs 2,3% for diarrhea and 5,7% vs 1,1% for nausea), pain in extremity (15,3% vs 6,8%), cardiac failure acute (13,6% vs 4,5%), syncope (3,4% vs 0%).

Cardiac failure acute in patients treated with tafamidis 80mg remained also higher through all treatment periods compared to patients treated with tafamidis 20mg. Frequencies of cardiac failure acute reported with tafamidis 80mg was similar to those reported with placebo (9,6%). This trend for acute cardiac failure with tafamidis 80mg is also observed in the Broad cohort (11,5% vs 5,2% with the 20mg).

Regarding treatment related hepatic events, "liver function test increased" was mostly reported with tafamidis 80mg compared to placebo and tafamidis 20mg (3,4% vs 0,6% vs 0% respectively). Gamma-glutamyltransferase was more reported with tafamidis (3,4% with tafamidis 80mg and 2,3% with tafamidis 20mg) compared to placebo (2,8%). Among the 19 hepatic events possibly related to tafamidis, 15 concerned patients treated with tafamidis 80mg (only 4 patients on tafamidis 20mg). The 2 reported case of dose interruption due to increase of liver function concerned patients treated with tafamidis 80mg. Hepatotoxicity is an important potential risk mentioned in the RMP of Vyndaqel and should continue to be closely monitored with tafamidis, especially with the high dosage.

One severe case of pancreatitis was reported with tafamidis 80mg.

A decrease of thyroxine level was mostly reported in the tafamidis 80mg arm (29,9%) compared to tafamidis 20mg arm (12,3%) or placebo arm (4,5%). Among the 7 cases of hypothyroidism, 5 concerned tafamidis 80mg. Changes in thyroid dysfunction are an important potential risk mentioned in the PGR of Vyndaqel 20mg and should continue to be closely monitored with tafamidis, especially with the high dosage.

- Safety of 20mg tafamidis:

Some adverse events were more reported with tafamidis 20mg compared to tafamidis 80mg: UTI (5,7% vs 2,3%), cardiac failure congestive (15,9% vs 11,9%), acute kidney injury (10,2% vs 7,4%).

3.5. Uncertainties and limitations about unfavourable effects

- Patients without symptoms of heart failure - NYHA Class I:

There is a risk of misuse in the elderly in the absence of clear diagnosis of ATTR-CM in patients without symptoms.

A Healthcare Professional Guide (HCP Guide) is proposed as a one-time distribution to all potential prescribers, including physicians knowledgeable in the management of patients with amyloidosis and/or cardiomyopathy, in each Member State where Vyndaqel 61 mg is launched for ATTR-CM.

Key message on the clinical criteria for the diagnosis of ATTR-CM in the HCP Guide were agreed and reflected in Annex II of the product information and the RMP.

The potential off-label use will be monitored in the THAOS registry, which will be extended to cardiac settings until 2023 and will allow to collect: additional safety data on patients with ATTR-CM, from all NYHA Class (including NYHA Class IV), and information regarding diagnosis criteria.

- New formulation of 61 mg tafamidis free acid: There is no possibility to reduce the dose in case of adverse events with the choice of a single high dose (61mg). However, both doses of tafamidis tested in main clinical study were relatively well tolerated.

3.6. Effects Table

Table 24: Effects Table

Effect	Short Description	Unit	Tafamidis 20 mg	Tafamidis 80 mg	Placebo	Uncertainties/ Strength of evidence	Reference
	Favourable Effects						
Finkelstein-Schoenfeld analysis P Win ratio			p=0.0006 1.695 (1.255;2.289)				Study B3461028
			p= 0.0048 1.81	p= 0.0030 1.64			
Mortality	Number of patients alive at month 30	% (HR)	70.5% (reduction of 30.2%) P=0.0259		57.1%	In NYHA class III, the rates of CV-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (76.9% vs 58.7%) and CV-related mortality tended to be higher with tafamidis compared to placebo (51.3% vs 49.2%)	
All-cause deaths		%	27.3% P= 0.1564	30.7% P= 0.0378	42.9%		
CV-related hospitalisations	Average frequency of CV Hospitalisations during 30 months (per patient per year) among those alive at Month 30	Per patient per year %	0.297 52.3% P<0.0001 (reduction of 32.4%)		0.455 60.5%		
			47.7% P= 0.0017	54.5% P= 0.0005	60.5%		
6MWT	Change from baseline to month 30 in 6MWT	m	-54.87 P<0.0001		-130.5		
KCCQ-OS score	Change from baseline to Month 30 in quality of life on the KCCQ-OS score		-7.16 P<0.0001		-20.81		
CV-deaths	Reduction	HR	(reduction of 30.9%) P=0.0383				
		%	21.6%	25.6%	35.6%		
TTR stabilisation			82.7%	87.8%		58.9% in variant 94.2% in wild	
NT-proBNP concentration	Value at M30	Pg/ml	2542	1371	3959		
	Difference	Pg/ml	-1417 P=0.0571	-2587 P<0.0001			
	Unfavourable Effects						
Cardiac failure	Incidence of cardiac failure	N (%)	30 (34.1)	46 (26.1)	60 (33.9)		Study B3461028
Fall	Incidence of fall	N (%)	27 (30.7)	43 (24.4)	41 (23.2)		
Dyspnoea	Incidence of dyspnoea	N (%)	21 (23.9)	29 (16.5)	55 (31.1)		

Atrial fibrillation	Incidence of atrial fibrillation	N (%)	16 (18.2)	35 (19.9)	33 (18.6)		
Constipation	Incidence of constipation	N (%)	14 (15.9)	26 (14.8)	30 (16.9)		
Diarrhoea	Incidence of diarrhoea	N (%)	10 (11.4)	22 (12.5)	39 (22.0)		
Nausea	Incidence of nausea	N (%)	9 (10.2)	20 (11.4)	36 (20.3)		
Asthenia	Incidence of asthenia	N (%)	11 (12.5)	18 (10.2)	11 (6.2)		
Fatigue	Incidence of fatigue	N (%)	16 (18.2)	29 (16.5)	33 (18.6)		
Oedema peripheral	Incidence of oedema peripheral	N (%)	17 (19.3)	30 (17.0)	31 (17.5)		
Bronchitis	Incidence of bronchitis	N (%)	9 (10.2)	21 (11.9)	19 (10.7)		
Pneumonia	Incidence of pneumonia	N (%)	10 (11.4)	23 (13.1)	17 (9.6)		
Upper respiratory tract infection	Incidence of upper respiratory tract infection	N (%)	7 (8.0)	17 (9.7)	16 (9.0)		
Urinary tract infection	Incidence of urinary tract infection	N (%)	9 (10.2)	16 (9.1)	27 (15.3)		
Fluid overload	Incidence of fluid overload	N (%)	13 (14.8)	19 (10.8)	29 (16.4)		
Gout	Incidence of gout	N (%)	10 (11.4)	18 (10.2)	29 (16.4)		
Pain in extremity	Incidence of pain in extremity	N (%)	6 (6.8)	27 (15.3)	20 (11.3)		
Balance disorder	Incidence of balance disorder	N (%)	2 (2.3)	15 (8.5)	2 (1.1)		
Dizziness	Incidence of dizziness	N (%)	17 (19.3)	25 (14.2)	37 (20.9)		
Insomnia	Incidence of insomnia	N (%)	12 (13.6)	20 (11.4)	22 (12.4)		
Cough	Incidence of cough	N (%)	16 (18.2)	21 (11.9)	30 (16.9)		
Hypotension	Incidence of hypotension	N (%)	12 (13.6)	19 (10.8)	19 (10.7)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given there are currently no approved specific pharmacological treatment for ATTR-CM, an ultimately fatal disease, there is a significant unmet medical need for an effective and safe treatment to slow the progression of disease and improve patient outcomes.

In this context, study B3461028 is the first phase 3 study demonstrating a reduction of all-cause mortality and cardiovascular-related hospitalisation in a selected population of patients with ATTR-CM.

The reduction of all-cause mortality at month 30 and frequency of CV-related hospitalizations per year can be considered of main importance. A relevant positive effect on walking function assessed with the 6MWT and on quality of life assessed with the KCCQ-OS score as key secondary endpoints is another point of interest for this degenerative disease, but the magnitude of the effect is more difficult to appreciate.

Regarding safety, overall, results demonstrate that oral tafamidis meglumine–dosed at either 20 mg or 80 mg once daily was well tolerated with a safety profile comparable to placebo in the target population. No major safety concerns were identified in patients with ATTR-CM treated with tafamidis as compared to the safety profile identified in ATTR-PN patients.

Efficacy results are consistent for both hereditary and wild-type ATTR-CM, but there is a tendency to higher clinical events and lower TTR stabilization in the variant TTR genotype group, compared to the wild-type TTR genotype group, that will need further assessment.

The severity of the disease can be distinguished between the variant and the wild-type forms. Indeed, when considering the mechanism of the disease, variant TTR is inherited by mutation in hereditary forms, while in wild-type forms, TTR is becoming unstable with age, without clear origin. Variant forms can be detected earlier, in a family context, even before the onset of cardiac symptoms, and can be associated with neurologic phenotype. Wild-type patients are around 75 year-old at diagnosis and are also associated with multiple non-cardiac symptoms such as deafness, carpa tunnel syndrome or lumbar canal stenosis, and may be common in the elderly population (>80-85 year-old). It seems that the evolution of the disease differs between these 2 types, with median survival of 25.6 months for variants and 43.0 months for wild-type.

Consequently, since the medical need may not be the same, with a more severe and evolutive disease in the variant patients, the management of patients may differ. In this context, TTR genotyping was added to section 4.2 of the SmPC among the assessment tools for diagnosis.

There are some uncertainties regarding patients with NYHA Class I. Indeed, the diagnosis ATTR-CM cannot be formally established without a number of specific procedures (biopsy, scintigraphy, TTR identification, genotyping). Such heavy clinical management could be questionable in patients without symptoms of heart failure, while a clinical benefit can be considered as expected, despite the weak number of included NYHA Class I patients in clinical pivotal study (<10%). There is a risk of misuse in the elderly in patients with signs of heart failure without ATTR-CM, which will be mitigated with the distribution of the Healthcare Professional Guide, intended to cardiologists, providing them the clinical criteria for the diagnosis of ATTR-CM and informing them about the importance to participate to the THAOS registry.

There are some uncertainties regarding the clinical benefit in the subgroup of NYHA Class III, since the tafamidis was not superior to placebo on the main clinical endpoints, which questions on the relevance of late treatment initiation (related to the severity of symptoms or age). In this context, the decision to

start or maintain treatment should be taken at the discretion of the cardiologist, as mentioned in section 4.2 of the SmPC.

Furthermore, it should be noted that the risk of off-label use cannot be considered low.

In this context, the key message on the clinical criteria for the diagnosis of ATTR-CM were revised in the Healthcare Professional Guide and the revised protocol of the THAOS registry will be submitted as post-authorisation measure in 2020.

The MAH has not provided fully convincing arguments to select 61 mg (80 mg equivalent) dose as compared to 20 mg regarding hard parameters of clinical efficacy. The selected approach regarding NT-proBNP and the other PK parameters related to TTR stabilization and fostered outcomes are not in line with what has been clinically observed in study B3461028. However, the 80 mg dose has the largest evidence base that is twice as large than for the 20 mg dose. Moreover, tafamidis was similarly well tolerated across both dose groups.

Therefore, considering also that there are no clear biomarker target levels, signs, or symptoms to steer dosing and the therapy has shown morbi/mortality benefit it is agreed that the 61mg dose is an appropriate dose in this particular context of severe and evolutive disease. The benefit-risk balance of the 61 mg dose was considered positive.

3.7.2. Balance of benefits and risks

The overall balance benefit risk of tafamidis to treat ATTR-CM patients is favourable from pooled tafamidis doses in the overall population, and tafamidis 80mg/61mg doses was considered effective in the claimed indication. The benefit-risk balance of the 61 mg dose is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Vyndaqel is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Vyndaqel is not similar to Onpattro and Tegsendi within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation from market exclusivity

Not applicable, since Vyndaqel is not deemed to be "similar" to any authorised orphan medicinal product.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Vyndaqel 61 mg soft capsules is favourable in the following indication:

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

The CHMP therefore recommends the extension of the marketing authorisation for Vyndaqel to introduce a new strength (tafamidis 61 mg soft capsules) and to introduce qualitative change in declared active substance (tafamidis) not defined as a new active substance subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of Vyndaqel (tafamidis) in each Member State, the MAH must agree on the content and format of the Healthcare Professional Guide, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Healthcare Professional Guide is aimed at raising prescribers awareness around:

- The need to counsel patients on appropriate precautions when using tafamidis, particularly the avoidance of pregnancy and the need to use effective contraception methods.
- Advising female patients to inform their doctor immediately in case of exposure to tafamidis during (or within 1 month prior to) pregnancy for physicians' reporting and assessment.
- Joining the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program in case of exposure to tafamidis during pregnancy to collect additional data on pregnancy outcome, birth, neonate/infant health and 12 month follow-up with milestones reached; details on how to report pregnancies for women receiving Vyndaqel (tafamidis) will be provided.
- Advising patients to contact their doctor about any adverse events while taking tafamidis and reminding physicians and pharmacists of the requirement to report suspected adverse reactions related to Vyndaqel (tafamidis).
- The clinical criteria for the diagnosis of ATTR-CM before prescribing tafamidis, to avoid administration to non-qualifying patients.

Encouraging patients to enter the Transthyretin-Associated Amyloidosis Outcome Survey (THAOS). Details will be provided on how to enrol patients into this international disease registry through participating sites (list of EU participating sites will be provided).

The MAH shall ensure that in each Member State where tafamidis is marketed, all Healthcare Professionals who are expected to prescribe tafamidis have access to/are provided with the following educational material:

The Healthcare Professional Guide with a list of EU participating sites for the Transthyretin-Associated Amyloidosis Outcome Survey (THAOS) study.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
Within the planned post-authorisation sub-study of the THAOS registry the MAH shall evaluate in non-V30M patients the effects of Vyndaqel on disease progression and its long term safety as detailed in a CHMP agreed protocol, and shall provide yearly updates on the collected data within the annual re-assessment.	Annual Reassessment

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Additional Data exclusivity/Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Pfizer Europe MA EEIG, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new

therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

This additional 1 year of marketing protection can only be granted if the authorisation of the variation related to this new indication is granted within the first 8 years of the 10 years of marketing protection.

However, for the present application, the period of the eight years has elapsed before the MAH obtained an authorisation for this new therapeutic indication which, during the scientific evaluation was considered to bring a significant clinical benefit in comparison with existing therapies and hence the additional 1 year of marketing protection cannot be granted.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Type II variation (C.I.4) to update Annex II to add to the key elements of the risk minimisation measures wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme and to update sections 2, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.1 and 6.5 of the SmPC of Vyndaqel (tafamidis meglumine) 20 mg soft capsules, Annex II and IIIA and IIIB to align it to Vyndaqel 61 mg soft capsule.

In addition, it was agreed to update to Section 16 Information in Braille of Annex IIIa - Labelling (carton) to differentiate between the dosage forms.

In addition, an updated RMP version 9.3 was agreed.

Appendices

1. CHMP AR on similarity dated 29 May 2019.
2. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 29 May 2019.