VYNDAQEL (TAFAMIDIS) RISK MANAGEMENT PLAN

RMP Version number: 10.0

Data lock point for this RMP: 16 Aug 2023

Date of final sign off: 04 December 2023

Rationale for submitting an updated RMP:

The purpose for submitting an updated RMP is the completion of the Category 3 studies B3461001 and B3461042. No new safety concerns or any change in characterization of existing risks was identified based on review of the studies. Studies B3461001 and B3461042 are removed as additional PV activities. The clinical and post-marketing exposure is updated per DLP of 16 August 2023.

Summary of significant changes in this RMP (version 10.0):

PART II. Module SI: Update data with DLP of 16 August 2023.

PART II. Module SIII: Update data with DLP of 16 August 2023.

PART II. Module SIV: Remove paternal exposure cases to align with SmPC and update maternal exposure per new DLP.

PART II. Module SV: Update data with DLP of 16 August 2023.

PART II. Module SVII: Delete justification of removal of important identified risks Urinary tract infection, Diarrhoea, Upper abdominal pain, Vaginal infection, the important potential risk of Hypersensitivity reactions and missing information safety and efficacy in elderly patients and Longer term safety. The PRAC has endorsed the removal of these safety concerns.

PART III: Removal of additional PV B3461001 and B3461042 for applicable risks.

PART V: Removal of additional PV B3461001 and B3461042 for applicable risks.

PART VI: Removal of additional PV B3461001 and B3461042 for applicable risks.

PART VII: Annex 2, Annex 3, Annex 6, Annex 7 and Annex 8 to the RMP.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 9.8

Approved with procedure: 27 July 2023

Date of approval (opinion date): EMEA/H/C/002294/IB/0088

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATTR	transthyretin amyloid
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTRm	variant transthyretin amyloid
ATTR-PN	transthyretin amyloid polyneuropathy
AUC	area under the concentration-time curve
AUC24	area under the concentration-time curve from time 0 to 24 hours
AUCinf	area under the concentration-time curve from time zero to infinity
BCRP	breast cancer resistant protein
CHF	congestive heart failure
CI	confidence intervals
CLcr	Creatinine Clearance
CL/F	apparent clearance
CM	cardiomyopathy
C_{max}	maximum plasma concentration
CSR	Clinical Study Report
CV	cardiovascular
CYP3A	Cytochrome P450, Family 3, Subfamily A, Polypeptide 4
EC	European Commission
EPAR	European Public Assessment Report
EU	European Union
FAP	familial amyloid polyneuropathy
FAPWTR	Familial Amyloidotic Polyneuropathy World Transplant Registry
FDA	Food and Drug Administration
GD	gestation day
GI	gastrointestinal
hATTR	hereditary transthyretin amyloidosis
HED	human equivalent dose
HLT	Higher Level Term
IBD	International Birth Date
Leu111Met	leucine replaced by methionine at position 111
LFT	liver function test
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MATE	multidrug resistance protein
mBMI	Modified Body Mass Index
MDR1	Multidrug resistance protein
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
n	sample size
N	no
N	number of subjects/patients
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	organic cation transporter
OLTX	Orthotopic Liver Transplantation

P-gp	P-glycoprotein
PBRER	Periodic Benefit Risk Evaluation Report
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PMS	post market surveillance
PSUR	Pharmacovigilance Safety Update Report
PT	Preferred Term
QD	once a day
QOL	quality of life
SAE	serious adverse event
SD	single dose
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOB	Specific obligation
SOC	System Organ Class
TESPO	Tafamidis Enhanced Surveillance Pregnancy Outcomes
THAOS	Transthyretin-Associated Amyloidoses Outcomes Survey
T_{max}	time to reach C_{max}
TSH	thyroid-stimulating hormone
TTR	transthyretin
TTR-FAP	transthyretin familial amyloid polyneuropathy
UGT	uridine 5'-diphospho-glucuronosyltransferase
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
vs	versus

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Tafamidis
Pharmacotherapeutic group(s) (ATC Code)	Other nervous system drugs ATC code N07XX08
Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	VYNDAQEL
Marketing authorisation procedure	centralised
Brief description of the product:	Chemical Class: Tafamidis (as the free acid): 2- (3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid Tafamidis meglumine: 2- (3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid mono (1-deoxy-1-methylamino-D-glucitol) Tafamidis meglumine is the meglumine salt form of tafamidis, the only active ingredient contained in tafamidis meglumine soft gelatin capsules.
	Summary of mode of action: Tafamidis is a specific stabilizer of transthyretin.
	Important information about its composition: N/A
Hyperlink to the Product Information:	Module 1.3.1 Summary of Product Characteristics, Labelling And Package Leaflet
Indication(s) in the EEA	Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy.
Dosage in the EEA	Tafamidis meglumine 20 mg (equivalent to 12.2 mg tafamidis) orally once daily Tafamidis 61 mg orally once daily
Pharmaceutical form(s) and strengths	Capsule, soft, 20 mg Capsule, soft, 61 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

SI.1. Epidemiology of the Disease

ATTR amyloidosis is a severely debilitating, and ultimately fatal, systemic condition induced by the accumulation of an insoluble fibrillar protein (ATTR) within tissues in amounts sufficient to impair normal function. Transthyretin is a transport protein of thyroxine and retinol-binding protein-retinol (vitamin A) complex[1,2] and is mostly produced by the liver. Misfolding and aggregation of ATTR can occur in the context of genetically normal (wild-type) protein or due to a substitution or deletion mutations in the transthyretin gene (variant) resulting in unstable transthyretin tetramers and monomer formation[3]. These monomers can misfold and self-aggregate in the extracellular space forming toxic intermediates that ultimately assemble into insoluble amyloid fibrils and which can result in progressive amyloid deposition in tissues.[4,5,6,7] This can occur in amounts sufficient to impair normal functioning.

The two major phenotypes which form the spectrum of ATTR amyloidosis are transthyretin amyloid polyneuropathy (ATTR-PN) which primarily affects the peripheral and autonomic nerves and is also referred to as transthyretin familial amyloid polyneuropathy (TTR-FAP), and transthyretin amyloid cardiomyopathy (ATTR-CM) which primarily affects the myocardium. These clinical manifestations may occur in isolation or together. Both result in progressively impaired function, and ultimately in death if not treated.

Vyndaqel is currently indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment and for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

SI.1.1. Transthyretin Amyloid Polyneuropathy (ATTR-PN)

Background:

ATTR-PN is a late onset, autosomal dominant disease characterised by inexorable neurodegeneration associated with sensory loss, motor weakness and autonomic dysfunction such as dizziness, gastrointestinal disorders, sexual dysfunction, urinary incontinence, and alternating diarrhoea and constipation.[8,9,10] ATTR-PN disease usually begins in the third decade of life (approximately ages 30 to 39 years), but the onset of symptoms can occur earlier or later.

Before tafamidis approval, the only demonstrated effective therapy for ATTR-PN is Orthotopic Liver Transplantation (OLTX), which removes the main production site of amyloidogenic mutant TTR protein and replaces it with the production of wild-type TTR.[11,12,13] The optimal impact of liver transplantation on the course of ATTR-PN is generally observed when the procedure is conducted early in the course of the disease. For patients with advanced-stage ATTR-PN, there is no survival benefit to transplantation compared with no transplant, thus underscoring the need for a treatment to stabilize the disease early while the deficits are still mild-to-moderate in severity.[14,15] For those patients

who receive a donor organ, transplantation is often associated with serious morbidity and mortality and life-long immunosuppression.

In 2018, the European Commission granted Marketing Authorisation in the EU to Tegsedi (inotersen; antisense oligonucleotide) for the "treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)") and Onpattro (patisiran; small interfering RNA) for the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy". In 2022, the European Commission granted Marketing Authorisation in the EU to Amvutra (vutrisiran; double-stranded small interfering RNA) for the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy". Of note, Pfizer considers tafamidis to offer significant benefit over these therapies for treating patients with ATTR-PN. Tafamidis is administered orally once daily and has a well characterised and favourable safety profile over 10 years of marketed use.

SI.1.1.1. Incidence and Prevalence

The global prevalence of ATTR-PN is estimated to be 5,000-10,000 but is potentially as large as over 38,000 patients[16]. Available reports [16,17] on the prevalence or incidence of ATTR-PN in the EU were applied to estimate the low, mid, and high country-specific and global ATTR-FAP population sizes by the varying of assumptions for the underlying risk of ATTR-FAP within populations (Table 1).

Table 1. Summary of the Available Prevalence of Transthyretin Familial Amyloid Polyneuropathy Patients in European Union Member States[a]

Country	General population, (Million)	Prevalence low	Prevalence mid	Prevalence high
Bulgaria	7.2	41	41	41
Netherlands	16.9	45	45	45
Cyprus	1.2	51	51	51
Germany	81.4	121	121	121
Sweden	9.8	253	253	253
France	66.8	502	502	502
Italy	60.8	500	550	600
Portugal	10.3	1990	2051	2111
Extrapolated				
Luxembourg	0.6	0	1	4
Slovenia	2.1	1	3	16
Ireland (North)	1.9	1	3	14
Finland	5.5	2	8	41
Denmark	5.7	2	8	43
Austria	8.6	3	13	65
Hungary	9.8	3	15	74
Czech Republic	10.6	3	16	79
Greece	10.8	3	16	81
Belgium	11.3	4	17	85
Romania	19.8	6	29	149
Poland	38.0	12	56	286
Spain	46.4	15	69	349
UK[b]	65.1	21	97	490

a. Source: Adapted from Schmidt et al.
b. At the time of publication, the UK was a member state of the European Union.

SI.1.1.2. Demographics of the Target Population–Age, Sex, Race/Ethnic Origin

Geographic distribution

There are two particularly endemic regions in the EU: the north of Portugal and the northernmost region of Sweden. Migrations of Portuguese are believed to have brought the mutation to Brazil and Argentina, with other foci of TTR Valine replaced by methionine in position 30 of TTR protein (Val30Met previously known as V30M, also referred as Val50Met) identified elsewhere (Majorca, Turkey, Italy, Cyprus, and Greece).[18] Val30Met is considered the major hereditary variant. Although also endemic in some areas of Japan, the prevalence of ATTR-PN is estimated to be lower than in Europe, at approximately one in 1,000,000 individuals[19]. Brazil is a country of Portuguese colonization and Portuguese descendants are estimated to be more than 25 million – which is more than the population of Portugal itself[20]. In Brazil, the population of ATTR-FAP cases is estimated to be around 5,000 patients[21,16]. Based on data from The Centro de Estudos de Paramiloidose Antônio Rodrigues de Mello (CEPARM, N=102), 77% cases were from Rio de Janeiro, 96% had Portuguese ancestry, 96% carry Val30Met mutation. Brazil also has the biggest Japanese colony outside Japan, but no cases of FAP has been reported in this population probably due to the origin from non-endemic areas in Japan. Patients with mutations other than Val30Met have been reported in many EU countries, including France, Germany, UK, Italy and Spain.[22,23]

Penetrance of the less common TTR mutations is more difficult to estimate, given the relatively small number of patients identified.

Age Distribution

ATTR-PN disease usually begins in the third decade of life (approximately ages 30 to 39 years), but the onset of symptoms may be earlier or later.[10] Early-onset ATTR-PN is typically considered at <50 years old while late-onset is considered at ≥50 years old. While ATTR-PN is an autosomal dominant disease, its phenotypic expression displays some variability. Based on Portugal's national centralized medical electronic prescription (MEP) database (ATTR-PN n=2,348), the seven-year (2010-2016) medium age-of-onset was 38 years old (IQR: 31-53), with 28.7% patients considered late-onset[24]. In Japan, onset of symptom peaked in the 30s to 40s, as well as in the 60s (bimodal distribution)[25]. In Sweden [29], symptom onset may peak at 50s or 60s (late-onset)[25]. Moreover, in non-endemic cases in France[26,27] , Italy[28] and Turkey[29], symptom onset may occur as late as in their 50s or 60s. In some of the other non-endemic regions, ATTR-PN patients also seem to be late-onset. In two studies conducted in the United States (US),[30,31] the mediun age at symptom onset was 53 and 64 years, respectively. In both studies, 38% and 41% of patients tested were identified with the Val30Met mutation, respectively. A heterogeneous clinical presentation has also been observed.[32] The clinical features in non-Val30Met patients in Japan were similar to those of late onset patients with the Val30Met variant. Of note, the late onset patients also had marked cardiac dysfunction, particularly in some TTR variant types (Asp18Glu and Ser50Ile)[33]. Important factors that contribute to heterogeneity include the specific TTR mutation, endemic as opposed to non-endemic geographic location, and the sex of the patient.[22]. Paediatric cases of ATTR-PN are rare. South Korea reported the first ATTR-PN

case in 2019 (age=17)[34]. No other published research papers or case report regarding pediatric ATTR-PN patients has been identified. [27]

Gender Distribution

Based on Portugal's national centralized MEP database (N=2,348), 56% of the patients were male[24]. Similarly, based on data from 1,233 patients diagnosed of familial amyloid polyneuropathy (FAP-type I) in north of Portugal, the ratio of male to female patients affected by ATTR-PN was reported to be 1.3:1.[35] Based on data from 59 Brazilian patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS), 58% patients were male[36].

Race and Ethnicity

As described above, there are two particularly endemic regions in the EU: the north of Portugal and the northernmost region of Sweden.

In the US, ATTR-PN is almost exclusively reported in TTR variants which are predominately found in the non-African-American population. In Brazil, the majority of patients were of Caucasian origin (81% based on 102 patients from CEPARM, and 66.7% based on 59 patients from the THAOS)[36].

SI.1.1.3. Risk Factors for the Disease

The underlying basis for the disease is a mutation in the TTR gene. Thus, there are no known modifiable risk factors for ATTR-PN.

SI.1.1.4. Main Treatment Options

Prior to 2018, the only available therapy for ATTR-PN, other than tafamidis, is OLTX, which removes the main production site of amyloidogenic mutant TTR protein and replaces it with a liver that produces wild-type TTR.[11,12,13] In 2018, the European Commission granted Marketing Authorisation in the EU to Tegsedi (inotersen; antisense oligonucleotide) for the "treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)") and Onpattro (patisiran; small interfering RNA) for the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy". In 2022, the European Commission granted Marketing Authorisation in the EU to Amvutra (vutrisiran; double-stranded small interfering RNA) for the "treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy". In the US, inotersen and patisiran have both been approved for ATTR-PN by the Food and Drug Administration (FDA). For patients with advanced-stage ATTR-PN, there is no survival benefit to transplantation compared with no transplant, thus underscoring the need for a treatment to stabilise the disease early while the deficits are still mild to moderate in severity.

SI.1.1.5. Morbidity and Mortality (Natural History)

ATTR-PN is invariably progressive and fatal. Survival for patients with ATTR-PN is severely shortened. After a mean survival ranging from 10-11 years from onset of initial symptoms for Val30Met mutations and variable survival (possibly ranging from 3-13 years)

for patients with non-Val30Met mutations,[22] patients usually die from progressive and relentless worsening of neuropathy, secondary infections, cachexia or sudden death.[10] Late-onset ATTR-PN is usually associated with development of CM and may have shorter survival than early-onset patients (8.8 years vs. 11.4 years after onset), based on data from 871 Portugal patients without any liver transplant or tafamidis treatment[37].

SI.1.2. Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM)

SI.1.2.1. Incidence and Prevalence

The prevalence of ATTR-CM in patients is not well-established. Based on data from multiple national population-based registers in four Nordic countries (Sweden, Norway, Finland, Denmark), the prevalence of ATTR-CM in 2018 across four countries was 3.3 per 100 000. More specifically, 1.4 cases per 100 000 in Denmark, 1.8 in Finland, 3.7 in Norway, and 5.0 in Sweden[38]. In Japan, the prevalence of wild type ATTR-CM ranged from 155.8 per million to 191.1 per million among adults; for mutations, estimates ranged from 3.2 per million to 5.1 per million[39]. Additional data on the prevalence of wild-type ATTR-CM is scarce. Studies using a non-biopsy approach to diagnosis[40,41] report a prevalence of 1.3- 17[42]% in heart failure patients with preserved ejection fraction,[43] 13 to 16% in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis,[44] and 5% of patients with presumed hypertrophic cardiomyopathy.[45] Hereditary ATTR-CM is a rare disease; its prevalence varies between regions due to geographical clustering of TTR mutations[46].

SI.1.2.2. Demographics of the Target Population – Age, Sex, Race/Ethnic Origin

Wild-type ATTR-CM is almost exclusively a disease of older adults with an average age at diagnosis of around 75 years[38,47,48.] In most of the studied cohorts and registries, most of patients are men and Caucasian, but whether this relates to a true disease predilection in this population or a referral bias is unknown[48].

According to national registries data in 2018, ATTR-CM prevalence was much higher in men (7.4 per 100,000) compared to women (2.5 per 100,000) in Sweden[38]. Across four Nordic countries, the majority of patients were men (69%); more specifically, the proportion of male ATTR-CM patients in Sweden was 70.1%, in Norway was 75.6%, in Finland was 50.5%, and in Denmark was 79.7%.[38]

ATTR-CM is associated with genetic variants of TTR such as Val122Ile, Leu111Met, Ile68Leu and Thr60Ala.[48] Several other mutations are associated with a mixed phenotype presentation with patients presenting with ATTR-PN and ATTR-CM. The Val122Ile mutation allele occurs in 3.3% to 4.0% of the US African-American population,[49,50] and <0.1% in other populations[51]. The phenotype is similar to wtATTR-CM in that it causes a late-onset restrictive cardiomyopathy with minimal neuropathy at an average age of onset of around 70 years, and a male preponderance[52]. The true penetrance of this mutation is unknown and clearly relates both to the age of ascertainment and the methodology used to define disease[48].

Thr60Ala (pT80A) is a variant originated in the Northern part of the Republic of Ireland and causes a mixed phenotype with a high rate of carpal tunnel syndrome as first manifestation and is second most common mutation in the United States that causes hATTR-

CM. Disease onset, particularly of neuropathy, can be earlier (fourth decade of life), with a male predominance of approximately 3:1[48].

Val30Met (pV50M) is the most common worldwide mutation and is the prototype for hATTR polyneuropathy, which is endemic in certain regions of Portugal, Japan, and Sweden. Val30Met, most common worldwide mutation leading to ATTR-PN, has a late-onset variant in nonendemic areas that can present with cardiac symptoms, including heart block and HF. Other important mutations that cause hATTR-CM are Leu111Met and Ile68Leu, which occur in Denmark and Italy, respectively[52].

SI.1.2.3. Risk Factors for the Disease

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 transthyretin protein, previously called senile systemic or senile cardiac amyloidosis.[53,54] The underlying basis for ATTR-CM due to variant TTR is a mutation in the TTR gene. Disease severity and age of onset varies among families, which suggests the possibility that some external factors (eg, environmental factors) may alter gene expression.[55] Currently there are no known modifiable risk factors for ATTR-CM due to either variant or wild type disease.

SI.1.2.4. Main Treatment Options

Tafamidis remains the only approved treatment for ATTR-CM. Adjunct therapy to manage ATTR-CM symptoms include diuretics and other guideline directed medical therapies to treat heart failure. Arrhythmias is managed with medications, pacemarker, and implantable cardioverter defibrillator per cardiology guidelines. Transplantation is usually reserved to patient's refractory to medical therapy. For some patients with variant type disease, orthotopic liver and/or heart transplant might be an option.[56] Transplantation of the liver removes the primary production site of amyloidogenic variant TTR protein.[57,58] 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. Unfortunately, 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.

SI.1.2.5. Morbidity and Mortality (Natural History)

ATTR-CM is usually diagnosed in advanced stages of the disease which contributes to a poor prognosis: typical survival without treatment extends just 2-6 years from the time of diagnosis.[59] Without treatment, medium survival of ATTR-CM after diagnosis in the four Nordic countries (N=1930) was suggested to be 30 months in a cohort of patients identified during 2008-2018[38]. Clinical progression and outcomes depends on fibril type (wild-type vs. genetic variant), the specific mutation, the patient's age at disease onset, and the disease stage at diagnosis. Without treatment, ATTR-CM leads to irreversible organ damage, most importantly heart failure and death.[59,60]

SI.2. Important Comorbidities found in the Target Population

Comorbidities were obtained from the studies identified from the literature search described in Section SI.1, and cited in Section SI.1.1 through Section SI.1.2. Based on the literature search results, the most important comorbidities for the relevant indications are shown in Table 2.

Table 2. Important Comorbidities Found in the Target Population

Indication	Important Comorbidities
Transthyretin Amyloid Polyneuropathy	Cardiovascular disorders (eg, heart failure, rhythm disturbance, hyperlipidaemia, other CVD)[8,61]; genitourinary disorders (eg, urinary retention, urinary incontinence)[8,10,61]; gastrointestinal disorders (eg, diarrhoea, constipation)[61]; depression[61]
Transthyretin Amyloid Cardiomyopathy	Cardiovascular disorders (eg, atrial fibrillation, hypercholesterolemia, hypertension, stroke)[62] Diabetes Gastrointestinal disorders (eg, diarrhoea, constipation)[61]; Renal impairment/failure Musculoskeletal (e.g. ostheoartitis, osteoporosis) Neuropathy (e.g polyneuropathy, autonomic dysfunction) Cancer Geriatric (frailty, cataracts, neurodegenerative disease, hearing loss) genitourinary disorders (eg, urinary retention, urinary incontinence[3,48]

Abbreviations: CVD = cardiovascular disease;

Module SII. Nonclinical Part of the Safety Specification

The safety profile of tafamidis was assessed in a series of nonclinical studies in mice, rats, rabbits, and dogs. A summary of the key findings is presented in Table 3.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
Toxicity: **Acute Toxicity** (including safety pharmacology studies) In the core GLP battery of safety pharmacology studies, no effects were observed on the central nervous, cardiovascular, and pulmonary systems. Clinical signs indicative of effects on respiratory and/or central nervous systems were observed in the single-dose dog cardiovascular/pulmonary safety pharmacology study and the repeat-dose toxicity studies at high exposures and at high margins above clinical exposures.	The nonclinical data did not identify any safety concerns for humans.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
Repeat-Dose Toxicity **Hepatotoxicity** Hepatic effects (increased liver weights, increased AST and/or ALT, hepatocellular hypertrophy, multinucleated giant cells, foci of cellular alteration, hepatocellular necrosis, and/or Kupffer cell pigmentation were observed in repeat-dose studies in mice, rats, and/or dogs. Liver effects were observed at exposures which were ≥2.5x the human exposure at a dose of 20 mg tafamidis meglumine and ≥0.7x the human exposure at a dose of 80 mg tafamidis meglumine. • **Acyl glucuronide formation** The acyl glucuronide form was the sole plasma metabolite found in humans and was found in all the species tested in the repeated dose toxicity programme (mice, rats and dogs).	The observed liver findings were largely consistent with induction of adaptive responses to xenobiotic exposure in rodents[63, 64, 65, 66] and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety. There is a theoretical risk that acyl glucuronide compounds can be associated with idiosyncratic drug reactions, particularly those associated with immune responses and hepatic toxicity.[67] The clinical relevance of this potential toxic mechanism seems low for tafamidis, given the predicted lack of reactivity for the acyl glucuronide from tafamidis (which is derived from benzoic acid), relative to other structural motifs,[68] the low extent of metabolism (based on PK data from clinical Studies Fx-002 and Fx1A-107), and the lack of clinical signal to date.
Genotoxicity Tafamidis was negative in genotoxicity studies.	Tafamidis is not expected to be genotoxic when used in humans.
Carcinogenicity Tafamidis was not carcinogenic in Tg rasH2 mice or in rats	Tafamidis is not expected to be carcinogenic when used in humans.
Reproductive and Developmental Toxicity Tafamidis did not affect mating or fertility and was not teratogenic in rats. In an embryo-foetal developmental study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-foetal survival, and reduction in foetal weights were observed at an AUC_{24} ratio of ≥7.2x and ≥2.1x, based on the human AUC at steady state at doses of 20 mg tafamidis meglumine and 61 mg tafamidis, respectively. In the rat pre- and postnatal development study, decreased pup survival and reduced pup weights were noted following maternal dose administration during pregnancy and lactation at doses of 15 and 30 mg/kg/day. Decreased pup weights in males were associated with delayed sexual maturation (preputial separation). Impaired performance in a water-maze test for learning and memory was observed at 15 mg/kg/day. The NOAEL for viability and growth in the F1 generation offspring following maternal dose administration during pregnancy and lactation was 5 mg/kg/day (human equivalent dose = 0.8 mg/kg/day), a dose approximately 4.6x and 0.9x the doses of 20 mg tafamidis meglumine and 61 mg tafamidis, respectively.	While nonclinical studies have shown developmental toxicity, there are no data on the use of tafamidis in pregnant women. Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
Safety Pharmacology In the core GLP battery of safety pharmacology studies, no effects were observed on the central nervous, cardiovascular, and pulmonary systems. Clinical signs indicative of effects on respiratory (laboured respiration/dyspnoea in mice) and/or central nervous systems (leg twitching, ataxia, head bobbing, and twitching in dogs, and decreased motor activity and seizure in mice) were observed in the dog cardiovascular/pulmonary safety pharmacology study and repeat-dose study in mice at high exposures and at high margins above clinical exposures.	The nonclinical data did not identify any central nervous, cardiovascular, or pulmonary system safety concerns relevant for humans.
Other toxicity-related information or data No effects were observed in the T-cell dependent antibody response in mice	The nonclinical data did not identify other toxicity-related safety concerns relevant for humans.
Lactation The administration of 14C-tafamidis meglumine to lactating female Sprague Dawley rats on Day 4 or 12 postpartum (LD 4 and LD 12, respectively), following a repeat daily oral gavage dose of tafamidis meglumine (15 mg/kg/day, initiated GD 7) demonstrated excretion in maternal milk of dose-related radioactive material.	From the results of nonclinical PK studies, it is expected that newborns/infants who are being breastfed by mothers receiving tafamidis may be exposed to tafamidis. The effect of such exposure is unknown and a risk to newborns/infants cannot be excluded.
Pharmacokinetic Drug-Drug Interaction Potential (Enzyme Mediated) Based on in vitro results, the potential for tafamidis to cause PK drug-drug interaction by inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 or induction of CYP1A2, is unlikely. Tafamidis may inhibit the intestinal activities of UGT1A1. Tafamidis did induce CYP2B6 and CYP3A4 in vitro, however 20 mg tafamidis meglumine did not significantly affect the PK 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. Low or no risk of clinically relevant effects on CYP2B6 and CYP3A4 induction is anticipated.[69]	The risk of tafamidis causing enzyme mediated PK drug-drug interaction is expected to be low in humans.
Pharmacokinetic Drug-Drug Interaction Potential (Transporter Mediated) Based on in vitro results, the potential for tafamidis to cause PK drug-drug interaction by inhibition of 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. Mechanistic static models were used to estimate the maximal increase in the plasma AUC of substrates of these transporters when co-administered with tafamidis. The maximal increase in plasma AUC of rosuvastatin due to inhibition of BCRP in the GI tract was estimated to be 92% when	Based on the criteria outlined in the EMA Guideline on the investigation of drug interactions (June 2012), tafamidis has the potential to inhibit BCRP (systemically and in the GI tract), OAT1, and OAT3 at clinically relevant concentrations.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
dosed with 20 mg/day tafamidis meglumine and 98% when dosed with 61 mg/day tafamidis. The maximal increase in AUC of OAT1 and OAT3 substrates was estimated to be less than 25% for both the 20 mg/day tafamidis meglumine and 61 mg/day tafamidis doses.	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AUC = Area under the concentration-time curve; BCRP = Breast cancer resistance protein; C_{max} = Maximum observed concentration; CYP = Cytochrome P450; GD = Gestation Day; GI = Gastrointestinal; GLP = Good Laboratory Practice; LD = Lactation Day; MATE = Multidrug and toxin extrusion protein; MDR = Multidrug resistance protein; NOAEL = No observed adverse effect level; OAT = Organic anion transporter; OATP = Organic anion transporting polypeptide; OCT = Organic cation transporter; PK = Pharmacokinetics; UGT = UDP-glucuronyltransferase.

Module SIII. Clinical Trial Exposure

Clinical trial exposure data are provided for studies as of 16 August 2023. The clinical trial exposure data are provided for 3 different pools of subjects.

- ATTR-PN studies: B3461020 (Fx-005), B3461021 (Fx-006), B3461022 (Fx1A 201), B3461023, B3461010, B3461029 and B3461078
- ATTR-CM studies: B3461025, B3461026, B3461028, B3461045, and B3461077
- ATTR amyloidosis: B3461001
- Healthy volunteers: B3461075, B3461095, B3461102 and B3461103

Table 4. Duration of Exposure With Tafamidis in Studies ATTR-PN B3461020, B3461021, B3461022, B3461023, B3461010, B3461029 and B3461078

Duration of Exposure	Patients	Person Time (years)[a]
< 1 Month	5	0.05
≥1 Month	186	652.76
≥3 Months	182	652.01
≥6 Months	177	650.13
≥12 Months	164	640.09
≥18 Months	144	612.74
≥24 Months	126	581.83
≥36 Months	106	534.20
≥48 Months	72	409.39
≥60 Months	46	296.69
Total (≥1 dose)	191	652.82

a. Years since first dose is defined as time from first dose to last dose ie, (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 5. Duration of Exposure With Tafamidis in Studies ATTR-CM B3461025, B3461026, B3461028, B3461045, and B3461077

Duration of Exposure	Patients	Person Time (years)[a]
< 1 Month	33	1.33
≥1 Month	1805	2877.09
≥3 Months	1752	2867.52
≥6 Months	1523	2779.90
≥12 Months	984	2379.19
≥18 Months	767	2109.51
≥24 Months	538	1720.23
≥36 Months	314	1176.71
≥48 Months	69	333.20
≥60 Months	11	83.84
Total (≥1 dose)	1838	2878.42

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 6. Duration of Exposure With Tafamidis in ATTR Amyloidosis Study B3461001[a]

Duration of Exposure	Persons	Person Time[b] (years)
≥1 Month	2332	7405.7
≥3 Months	2281	7396.2
≥6 Months	2131	7338.0
≥12 Months	1858	7137.4
≥18 Months	1611	6833.9
≥24 Months	1354	6384.5
≥36 Months	929	5343.2
≥48 Months	638	4343.4
≥60 Months	492	3694.8
Total (≥1 dose)	2399	7406.8

a. This population is defined as those patients with any tafamidis treatment exposure from the time they were enrolled in THAOS, excluding time during clinical trial /compassionate use participation.
b. Duration of exposure (in years): Sum of all non-missing days when tafamidis was taken (excluding days of other clinical trial/compassionate use participation) / 365.25.

Table 7. Duration of Exposure With Tafamidis in Healthy Volunteer Studies B3461075, B3461095, B3461102 and B3461103

Duration of Exposure	Persons	Person Time (years)[a]
<1 Month	2	0.16
≥ 1 Month	67	9.40
Total (≥1 dose)	69	9.56

a. Duration of exposure is calculated as sum of the durations of individual periods in which subject has taken Tafamidis dose i.e. sum(next period Tafamidis dose start date - current period Tafamidis does start date + 1)/365.25. For last period; the duration of exposure is calculated as the duration from the start date of Tafamidis in the last period to subject's last contact date i.e. (last contact date - last period Tafamidis dose start date + 1)/365.25.

Table 8. Exposure by Age Group and Gender for Patients Treated With Tafamidis in ATTR-PN Studies B3461020, B3461021, B3461022, B3461023, B3461010, B3461029 and B3461078

Age Group	Female		Male		Total	
	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]
<65 years	79	286.94	83	273.65	162	560.58
≥65 years	9	29.72	20	62.51	29	92.23
Total	88	316.66	103	336.15	191	652.82

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 9. Exposure by Age Group and Gender for Patients Treated With Tafamidis in ATTR-CM Studies B3461025, B3461026, B3461028, B3461045, B3461077

Age Group	Female		Male		Total	
	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]
<65 years	23	39.07	145	226.27	168	265.34
≥65 years	174	268.31	1496	2344.77	1670	2613.08
Total	197	307.38	1641	2571.04	1838	2878.42

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 10. Exposure by Age Group[a] and Gender for Patients Treated With Tafamidis in ATTR Amyloidosis Study B3461001

Age Group	Male		Female		Total	
	Persons[b]	Person Time[c] (years)	Persons[b]	Person Time[c] (years)	Persons[e]	Person Time[d](years)
<65 years	633	2399.9	580	2582.5	1213	4982.4
≥65 years	983	1892.0	203	532.4	1186	2424.4
Total[d]	1616	4291.9	783	3114.9		

a. Patient's age group is categorized at the day-level, which means patients may appear in both <65 and ≥65 years old categories as they age.
b. This population is defined as those patients with any tafamidis treatment exposure from the time they were enrolled in THAOS, excluding time during clinical trial/compassionate use participation.
c. Duration of exposure (in years): Sum of all non-missing days when tafamidis was taken (excluding days of other clinical trial/compassionate use participation) / 365.25.
d. To calculate Total Persons, patients are only counted once although they may appear in more than one age category.
e. This population is defined as those patients with any tafamidis treatment exposure from the time they were enrolled in THAOS, excluding time during clinical trial/compassionate use participation.

Table 11. Exposure by Age Group and Gender for Patients Treated With Tafamidis in Healthy Volunteers Studies B3461075, B3461095, B3461102 and B3461103

Age Group	Female		Male		Total	
	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]	Persons	Person Time (years)[a]
<65 years	7	0.99	60	8.23	67	9.21
≥65 years	1	0.17	1	0.18	2	0.35
Total	8	1.16	61	8.40	69	9.56

a. Duration of exposure is calculated as sum of the durations of individual periods in which subject has taken tafamidis dose i.e. sum(next period Tafamidis dose start date - current period tafamidis does start date + 1)/365.25. For last period; the duration of exposure is calculated as the duration from the start date of tafamidis in the last period to subject's last contact date i.e. (last contact date - last period tafamidis dose start date + 1)/365.25.

Table 12. Dose of Treatment With Tafamidis in ATTR-PN Studies B3461020, B3461021, B3461022, B3461023, B3461010, B3461029 and B3461078

Dose of Exposure	Patients	Person Time (years)[a]
20 mg	191	652.82
Total	191	652.82

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 13. Dose of Treatment With Tafamidis in ATTR-CM Studies B3461025, B3461026, B3461028, B3461045, B3461077

Dose of Exposure	Patients	Person Time (years)[a]
20 mg	152	383.36
80 mg	228	481.08
61 mg	1458	2013.98
Total	1838	2878.42

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 14. Dose of Treatment With Tafamidis in ATTR Amyloidosis Study B3461001

Dose of Exposure	Persons[a]	Person Time[b] (years)
20 mg[c]	1537	5935.1
61/80 mg[d]	658	1043.1
Switched from 20 mg to 61/80 mg[e]		
20 mg	178	207.8
61/80 mg	170	209.6
Other[f]	9	11.2
Total[g]	2399	7406.8

a. This population is defined as those patients with any tafamidis treatment exposure from the time they were enrolled in THAOS, excluding time during clinical trial/compassionate use participation.
b. Duration of exposure (in years): Sum of all non-missing days when tafamidis was taken (excluding days of other clinical trial/compassionate use participation) / 365.25.
c. Patients who started with 20 mg and remained with 20 mg.
d. Patients who started with 61/80 mg and remained in 61/80 mg.
e. Patients who switched from 20 mg to 61/80 mg.
f. Subjects who received any other dose of tafamidis.
g. To calculate Total Persons, patients are only counted once although they may appear in more than one dose group. To calculate Total Person Time, total duration of a patient per dose group is summed

Table 15. Dose of Treatment With Tafamidis in Healthy Volunteers Studies B3461075, B3461095, B3461102 and B3461103

Dose of Exposure	Patients	Person Time (years)[a]
12.2 mg	56	6.55
20 mg	34	1.74
61 mg	12	1.27
Total	69	9.56

a. Duration of exposure is calculated as sum of the durations of individual periods in which subject has taken tafamidis dose i.e. sum(next period Tafamidis dose start date - current period tafamidis does start date + 1)/365.25. For last period; the duration of exposure is calculated as the duration from the start date of tafamidis in the last period to subject's last contact date i.e. (last contact date - last period tafamidis dose start date + 1)/365.25.

Table 16. Exposure by Ethnic or Racial Origin for Patients Treated With Tafamidis in ATTR-PN Studies B3461020, B3461021, B3461022, B3461023, B3461010, B3461029 and B3461078

Ethnic/Racial Origin	Persons	Person Time (years)[a]
Asian	29	45.90
Caucasian	130	481.12
Latino American	28	121.14
Not available	4	4.65

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 17. Exposure by Ethnic or Racial Origin for Patients Treated With Tafamidis in ATTR-CM Studies B3461025, B3461026, B3461028, B3461045, B3461077

Ethnic/Racial Origin	Persons	Person Time (years)[a]
White	1494	2454.29
Black	45	73.48
Black or African American	139	124.48
Asian	138	193.34
Other	22	32.84

a. Years since first dose is defined as time from first dose to last dose i.e. (last dose date - first dose date + 1)/365.25 by excluding the gap between parent and extension.

Table 18. Exposure by Ethnic or Racial Origin for Patients Treated With Tafamidis in ATTR Amyloidosis Study B3461001

Ethnic/Racial Origin	Persons[a]	Person Time[b] (years)
Caucasian	1112	2637.7
Afro-Caribbean	2	2.2
American Hispanic	7	16.2
Latino American	12	15.9
Asian	119	294.9
Black or African American	68	103.3
Other	17	40.1
Not Provided	1062	4296.6

a. This population is defined as those patients with any tafamidis treatment exposure from the time they were enrolled in THAOS, excluding time during clinical trial/compassionate use participation.
b. Duration of exposure (in years): Sum of all non-missing days when tafamidis was taken (excluding days of other clinical trial/compassionate use participation) / 365.25.

Table 19. Exposure by Ethnic or Racial Origin for Patients Treated With Tafamidis in Healthy Volunteers Studies B3461075, B3461095, B3461102 and B3461103

Ethnic/Racial Origin	Persons	Person Time (years)[a]
Asian	6	0.96
Black or African American	21	2.96
Multiple	1	0.14
White	41	5.49

a. Duration of exposure is calculated as sum of the durations of individual periods in which subject has taken tafamidis dose i.e. sum (next period Tafamidis dose start date - current period tafamidis does start date + 1)/365.25. For last period; the duration of exposure is calculated as the duration from the start date of tafamidis in the last period to subject's last contact date i.e. (last contact date - last period tafamidis dose start date + 1)/365.25.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Hypersensitivity to tafamidis or to any of the excipients listed on Section 6.1 of the label are the only contraindication included in the labelling.

Table 20. Exclusion Criteria That Are Not Proposed to Remain as Contraindications

Criteria	Reason for Exclusion	Is it to be considered Missing Information / Rationale
Disease-Primary or secondary amyloidosis.	Tafamidis is only active against amyloidosis affecting a specific protein (TTR).	No. Product labelling is clear about the target patient population for treatment with tafamidis.
Concomitant medical conditions-Patients with abnormal LFT results, prior liver or heart transplant, patients with significant cardiovascular abnormalities. Subjects with other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.	To more easily discern the safety and efficacy of tafamidis against a background of patients with limited concomitant medical issues.	Yes. "Severe hepatic impairment" is listed as missing information.
Viral screening-Positive results for HBsAg, anti-HCV, and/or HIV.	To more easily discern the safety and efficacy of tafamidis against a background of patients with limited concomitant medical issues, specifically diseases with potential implications for liver transplantation.	No. No specific safety or efficacy issues are anticipated in this patient group.
Substance abuse-Active alcohol or substance abuse within 60 days before Baseline (Day 0).	To avoid unreliable data collection and potential end organ damage resulting in difficulties in interpreting safety data.	No. These will not likely occur commonly in the general population and are not expected to pose an additional substantial risk.
Medications Use of protocol-prohibited NSAIDs, defined as greater than 3-4 times/month (acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac will be permitted). Subjects requiring treatment with calcium channel blockers (eg verapamil, diltiazem) or digitalis. Prohibited use of patisiran within 30 days prior to enrolment, or	To limit factors that may interfere with interpretation of positive or negative effects of tafamidis. Digitalis and calcium channel blockers (eg verapamil, diltiazem) are prohibited concomitant medications because they bind to amyloid fibrils and may lead to increased toxicity (Gertz 1985, Rubinow 1981, Rapezzi 2010).	No. Use of these medications will likely occur commonly in the general population and are not expected to pose an additional substantial risk.

Table 20. Exclusion Criteria That Are Not Proposed to Remain as Contraindications

Criteria	Reason for Exclusion	Is it to be considered Missing Information / Rationale
inotersen within 6 months prior to enrolment.		
Special populations-Pregnancy and breastfeeding.	Unknown reproductive toxicity and potential exposure via breast milk indicated from nonclinical studies.	No. "Reproductive and developmental toxicity an lactation" are already listed as Important Potential Risk.
Special populations-Children under 18 years of age.	ATTR-PN symptomology generally does not present until the third decade of life (also see discussion below). A literature search showed 0.12% of ATTR-PN patients were d <18 years of age. ATTR-CM is not expected in patients <18 years of age.	No. Product prescribing information is clear about the target population suitable for treatment with tafamidis.
Concomitant medical conditions-Other causes of sensorineuropathy.	To limit use to patients with indicated disease.	No. Product prescribing information is clear about the target population suitable for treatment with tafamidis.
Subjects with heart failure that, in the opinion of the investigator, is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzymes and ECG changes), or uncorrected valvular disease and not primarily due to transthyretin amyloid cardiomyopathy.	To limit use to patients with indicated disease.	No. Product prescribing information is clear about the target population suitable for treatment with tafamidis.
Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation. or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker is indicated but will not be placed.	To more easily discern the safety and efficacy of tafamidis against a background of patients with limited concomitant medical issues.	No. No specific safety or efficacy issues are anticipated in this patient group.
Subjects with renal failure requiring dialysis and/or have an estimated glomerular filtration rate (eGFR) of < 25 mL/min./1.73 m^2	To more easily discern the safety and efficacy of tafamidis against a background of patients with limited concomitant medical issues.	No. Tafamidis is excreted via the hepatobiliary pathway; therefore, dosage adjustment in patients with renal impairment is not necessary.

Table 20. Exclusion Criteria That Are Not Proposed to Remain as Contraindications

Criteria	Reason for Exclusion	Is it to be considered Missing Information / Rationale
Subjects who have symptoms indicative of New York Heart Association Classification IV at the Screening or Baseline visit.	To more easily discern the safety and efficacy of tafamidis against a background of patients with limited concomitant medical issues.	Yes. Data collected in patients with New York Heart Association Classification IV is limited. Patients in NYHA IV usually are considered for end stage HF therapies instead.

Anti-HCV = Anti-Hepatitis C Virus; HBsAg = Hepatitis B Surface Antigen; HIV = Human Immunodeficiency Virus; LFT = Liver Function Test; NSAID = Nonsteroidal Anti-Inflammatory Drug; TTR = Transthyretin; ATTR-PN = Transthyretin Amyloid Polyneuropathy.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 21. Limitations of Adverse Drug Reaction Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
That are uncommon	137 subjects treated with tafamidis have been studied in pivotal safety and efficacy studies in the clinical program for ATTR-PN. 377 subjects treated with tafamidis have been studied in pivotal safety and efficacy studies in the clinical program for ATTR-CM	Uncommon or rare adverse reactions to tafamidis are unlikely to have been identified in clinical studies.
In other patient populations	Subjects in clinical trials must meet entry criteria and thus are relatively homogeneous and may differ from the patient population who receive marketed drug.	ATTR-PN and ATTR-CM are endemic in certain geographical populations, but may occur in other populations that were less represented in the clinical trials.
Due to limited active drug data compared with placebo	In ATTR-PN population, only 1 double-blind, placebo-controlled study (Fx-005), of 18 months duration, including 65 patients treated with tafamidis and 63 receiving placebo. In ATTR-CM population, only 1 double-blind, placebo-controlled study (B3461028), of 30 months duration, including 264 patients treated with tafamidis and 177 receiving placebo.	Limited placebo-controlled data make it more challenging to identify adverse reactions in clinical trials

ADR = Adverse Drug Reaction; ATTR-PN = Transthyretin familial amyloid polyneuropathy; ATTR-CM = Transthyretin amyloid cardiomyopathy.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 22. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Female patients who were pregnant or lactating were excluded from all clinical trials in the development programme of tafamidis. There are no adequate data on the use of tafamidis in pregnant women. Studies in animals have shown reproductive toxicity. There was no evidence of adverse effects of tafamidis on fertility or reproductive performance in the rat. 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). Post-natal mortality and developmental anomalies were observed in rats at dose levels ≥12X the clinical dose. 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. To monitor outcomes of pregnant women with exposure to tafamidis, a TESPO programme was established to collect follow-up information up to 12 months post-delivery of babies potentially exposed to tafamidis via the mother while in utero. Medical or healthcare professionals are encouraged to report pregnancies occurring in women who are being treated with tafamidis by contacting the MAH. As of 31 August 2023, there were a total of 20 cases of maternal exposure in utero to tafamidis, including Maternal exposure during pregnancy (16 cases with 2 for a twin pregnancy), Maternal exposure time unspecified (2), Drug exposure before pregnancy (1) and Exposure during pregnancy (1). These 20 cases represented 19 pregnancies (1 twin pregnancy) and 20 foetus exposure, for which pregnancy outcome was reported as follow: 13 normal newborns (including 1 low birth weight and 1 pre-term infant), 1 live birth without other information, 2 with unknown outcome, 2 medical termination (twin pregnancy), and 2 voluntary terminations. For the medical terminations, intense vaginal haemorrhage occurred during 1st trimester in a 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. Of the 14 live births for infants exposed to tafamidis in utero, 5 provided post-natal follow-up at 6 months and 4 provided follow-up at 12 months (TESPO programme), reporting that the infants survived the first year of life and met their age-appropriate development milestones. No infant reported any congenital malformations/anomalies. The SmPC (Section 4.6) includes information noting that contraceptive measures should be used by women of childbearing potential during treatment with Vyndaqel and for 1 month after stopping treatment, due to the prolonged half-life. Section 4.6 also indicates that there are no substantial data on the use of Vyndaqel in pregnant women and that Vyndaqel should not be administered to pregnant women.

Table 22. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Breastfeeding women	The effect of Vyndaqel on nursing infants after administration to the mother has not been studied. No information is available on the presence of tafamidis in human breast milk. However, animal data demonstrate that Vyndaqel is secreted in the milk of lactating rats. The SmPC (Section 4.6) includes language noting that Vyndaqel should not be used while breastfeeding.
Patients with relevant co-morbidities: Patients with hepatic impairment	In the pivotal clinical trials, patients were excluded if they had ALT and/or AST values more than twice the ULN that was also considered by the investigator to be due to reduced liver function or active liver disease. The lower systemic exposure and increased apparent clearance observed in subjects with moderate hepatic impairment compared with healthy subjects (Study Fx1A-105) would not mandate a change in dosing regimen, as it is expected that the stoichiometry of tafamidis with its target protein TTR would be sufficient for stabilisation of the TTR tetramer. Part 2 of Study Fx1A-105 included the PKs of tafamidis in subjects with mild hepatic impairment. No differences in tafamidis exposure were identified between subjects with mild hepatic impairment and healthy subjects. The SmPC (Section 4.2) includes information that no dosage adjustment is required for patients with mild or moderate hepatic impairment and that Vyndaqel has not been studied in patients with severe hepatic impairment therefore caution is recommended.
Patients with renal impairment	Tafamidis has not specifically been evaluated in patients with severe renal impairment. A review of the effects on renal function and potential need for dosage adjustments is relevant because in later stages of ATTR-PN up to 30% of patients present with significant renal function impairment (eg, proteinuria), however only 10% progress to renal failure. The clinical study protocols in ATTR-PN populations excluded patients with CLcr <30 mL/min. In the pivotal randomised study (Fx-005) 2 patients had CLcr <50 mL min and 10 patients had CLcr between 50 and 80 mL/min. In the overall safety population (N = 127) there were a total of 3 patients with CLcr <50 mL/min and 29 patients with CLcr between 50 and 80 mL/min. There were 23 patients from completed Studies Fx-005, Fx1A-201, and Fx1B-201, contributing a total of 107 observations (<4% of the database), who had CLcr ≤50 mL/min (range 20 to 50 mL/min). The effect of CLcr was tested as a categorical covariate on CL/F (either ≤50 or >50 mL/min). The typical estimate of CL/F for subjects with CLcr >50 mL/min was 0.385 (95% CI: 0.369, 0.401) L/h. The typical change in CL/F in the 23 subjects with CLcr ≤50 mL/min was 24% lower (95% CI: 14-34%) than in patients with CLcr >50 mL/min. Although this change was estimated with good precision (percent RSE = 6.89%), this finding should be treated with caution given the small number of patients with CLcr <50 mL/min in the PK database. However, it does suggest that dose adjustment in patients with more severe renal dysfunction (CLcr <50 mL/min) is not required.

Table 22. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
	In the pivotal ATTR-CM clinical study (B3461028), patients with renal failure requiring dialysis and/or had an estimated glomerular filtration rate (eGFR) of <25 mL/min./1.73 m^2 were excluded. It is unlikely that renal impairment would impact the PKs of tafamidis, as tafamidis is primarily metabolised and excreted via the hepatobiliary pathway. The effects of CLcr on tafamidis PK were evaluated in the population PK analysis; PK estimates indicated no difference in steady-state clearance of tafamidis in patients with CLcr <80 mL/min compared to those with CLcr >80 mL/min. Therefore, dosage adjustment in patients with renal impairment is not necessary. The SmPC (Section 4.2) includes information that no dosage adjustment is required for patients with renal impairment.
Patients With Significant Cardiovascular Conditions	Patients with New York Heart Association classification III or IV were excluded from tafamidis ATTR-PN clinical trials. Other cardiac conditions were not excluded from the clinical studies. This is relevant because ATTR-PN may also include cardiac involvement, manifested as conduction disturbances often requiring pacemaker insertion, and restrictive CM, which manifests later in the disease.[8] Approximately 5% to 10% of patients with Val30Met ATTR-PN in completed tafamidis studies had cardiac involvement as assessed by presence of increased ventricular wall thickness (a surrogate for cardiac amyloid deposition). In contrast, the 21 non-Val30Met ATTR-PN patients enrolled in Study Fx1A-201 had a much higher prevalence of cardiac involvement (13/21, 62%). In addition, compared to the Val30Met patients these patients were older, had longer disease duration, more severe disease, and worse quality of life at baseline. Non-Val30Met patients enrolled in Study Fx1A-201 had at least one echocardiographic abnormality at baseline. The most commonly reported echocardiographic abnormalities at baseline were left ventricular posterior wall thickness and left ventricular septal thickness (≥13 mm), which were reported for 17 (89.5%) patients each, and "valve thickening," reported for 16 (84.2%) patients. These abnormalities indicate the presence of cardiac amyloid deposits and restrictive/hypertrophic CM. However, the AEs reported in Study Fx1A-201 were similar to those reported in Study Fx-005 and/or Fx-006, indicating that the tafamidis safety profile was similar in all patients with ATTR-PN, including those who also had cardiac involvement. A notable difference between the Val30Met and non-Val30Met patients was a higher incidence of falls reported in patients in Study Fx1A-201 (5/21 patients; 23.8%) which is likely related to the relative older age of these patients (mean age 65 years) and their substantial neurologic and cardiac disabilities. Study Fx1B-201 recruited patients with ATTR-CM, thus all 35 patients had a significant degree of cardiac impairment. Thirty-one (31) of the patients who completed Study Fx1B-201 continued to receive tafamidis in extension Study Fx1B-303 (B3461026), which is ongoing. In the pivotal ATTR-CM clinical study (B3461028), patients with New York Heart Association classification IV were excluded. At Baseline, 186 (70.5%) and 78 (29.5%) of patients in the pooled tafamidis group were NYHA Class I and II combined and Class III, respectively. For the placebo group, 114 (64.4%) and 63 (35.6%) of subjects were NYHA Class I and II combined and Class III, respectively.

Table 22. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients With a Disease Severity Different From That Studied in the Clinical Trials	As tafamidis represents a disease modifying approach, initiation of treatment relatively early in the disease at a time when treatment would be expected to impact the course of neuropathy is important. Therefore, patients with relatively early disease were enrolled into the clinical trials (Stage 1 or Stage 2). The median duration of symptoms at enrolment for the overall tafamidis population in pooled data from Studies Fx-005, Fx-006, and Fx1A-201 was 35.6 months. The median duration ranged from 28.9 months (subjects assigned to tafamidis) and 21.6 months (subjects assigned to placebo) in Study Fx-005 to 46.2 months for subjects in Study Fx1A-201. There are limited data on the effect of tafamidis in patients with more severe ATTR-PN (particularly Stage 3). As described in the literature, patients with more severe disease have poorer outcomes following liver transplant. Reports from Sweden demonstrated that the worst prognosis post-liver transplantation was observed in patients with more severe disease, poor nutritional status (low mBMI), and advanced age.[70,71,72] These results were also observed by Adams in French patients, in whom the presence of severe sensory, motor, and autonomic neuropathies were predictors of mortality.[73] Based on these data, inclusion/exclusion criteria in the tafamidis clinical trials were designed to enrol patients who were relatively early in their disease, ie, at a stage in which there was neurologic function to be maintained. The indication for marketed tafamidis in the EU specifies patients with Stage 1 symptomatic polyneuropathy, and thus if later stages of the disease were reported, this would be captured as off-label use.
Immuno-compromised patients	Not included in the clinical development programme.
Patients of Different Racial and/or Ethnic Origin	In the pivotal ATTR-PN clinical study (Fx-005), which was conducted in Europe and South America, 56 of 64 (87.5%) tafamidis-treated patients were of Non-Latino Caucasian origin, 6 (9.4%) were of Latino American origin and the ethnic origin of the last 2 patients (3.1%) was not known. Study B3461010 was conducted in Japan and evaluated treatment with tafamidis 20 mg in Japanese patients with ATTR-PN. Ten (10) Japanese patients were enrolled and treated with tafamidis for up to 12 months. In the global pivotal ATTR-CM clinical study (B3461028) conducted in the United States, Europe, Japan, Canada, and South America 211 of 264 (79.9%) of tafamidis-treated patients were White, 37 (14%) Black, 13 (4.9%) Asian and 3 (1.1%) Other race. There were 201 (76.1%) wild-type TTR and 63 (23.9%) variant TTR genotype subjects in the pooled tafamidis group. The most common TTR variant genotype across all groups was V142I/V122I (38 [14.4%] and 23 [13.0%] subjects in the pooled tafamidis and placebo groups, respectively).
Sub-Populations Carrying Known and Relevant Polymorphisms	Tafamidis is metabolised by Phase 2 glucuronidation, with UGT 1A1, UGT 1A3 and UGT 1A9 the major isoforms responsible for the in-vitro formation of the acyl glucuronide metabolite. Given the multiple enzymes involved, it is unlikely that polymorphism of any 1 of these enzymes would impact the metabolism of tafamidis.

Table 22. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Other Paediatric patients	There is no experience in the use of tafamidis in paediatric patients (less than 18 years of age). The youngest patient in the tafamidis clinical trial population was 24 years old at the time of enrolment. The intended population for tafamidis is adult ATTR patients with symptomatic polyneuropathy or cardiomyopathy. ATTR amyloidosis is a late onset disease and it is extremely rare for a patient with ATTR-PN to present with symptoms that may be attributable to the disease before the age of 18 years. In a literature review carried out for the PIP a conservative estimate of incidence in paediatric patients was calculated to be 0.12% (4 out of 3189 cases found in the literature) of the ATTR-PN population,.[27] The sponsor's request for a waiver of the requirement to submit a PIP was approved by the Paediatric Committee on 11 June 2010 (EMEA-000884-PIP01-10).
Patients With Amyloidosis Due to Proteins Other Than TTR	Patients with amyloidosis due to proteins other than TTR (including primary and secondary amyloidosis) were excluded from the tafamidis studies as tafamidis is a very specific and selective binder of TTR and would not be anticipated to be effective in conditions not associated with TTR. Therefore, tafamidis is specifically indicated in patients whose amyloidosis is associated with TTR. Use in patients with amyloidosis due to proteins other than TTR is unlikely.

AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Transaminase; ATTR = Transthyretin Amyloidosis; CI = Confidence Interval; CL/F = Apparent Oral Clearance; CLcr = Creatinine Clearance; CM = Cardiomyopathy; EU = European Union; MAH = Marketing Authorisation Holder; mBMI = Modified Body Mass Index; PIP = Paediatric Investigation Plan; PK = Pharmacokinetic; RSE = Relative Standard; SD = Standard Deviation; SmPC = Summary of Product Characteristics; TESPO = Tafamidis Enhanced Surveillance Pregnancy Outcomes; THAOS = Transthyretin Amyloidosis Outcomes Survey; TTR = Transthyretin; ATTR-CM = Transthyretin Amyloid Cardiomyopathy; ATTR-PN = Transthyretin Amyloid Polyneuropathy; ULN = Upper Limit of Normal; V122I = Valine replaced by isoleucine in position 122 of TTR protein; Val30Met = Valine replaced by methionine in position 30 of TTR protein (also Val30Met).

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

The worldwide exposure estimate to Tafamidis is based on audited pharmacy and/or wholesaler sales of Tafamidis received from IQVIA (formerly IMS Health) database. The marketing experience information is based on the number of standard units (SUs) sold from the International Birth Date (IBD) November 2011 to 16 August 2023. The SUs for 1 July 2023 to 16 August 2023 have been extrapolated by using the growth rate of previous quarter.

SV.1.2. Exposure

Cumulative exposure to marketed Tafamidis is estimated to be 86,373 patient-years. All patients were treated for TTR-FAP. This estimation is based on the following information:

- An estimated sales volume of 14,883,192 units from European1 commercial sales and 16,664,411 units from ROW2 (including Japan) for a total of 31,547,603 units from IBD to 16 August 2023.
- A daily regimen of 1 SU.
- The total SUs was divided by 365.25 to obtain patient-years.

Cumulative estimated exposure by indication and region based on or extrapolated from, as applicable data provided by IQVIA for the period IBD to 16 August 2023, is summarized in below.

Table 23. Cumulative Estimated Exposure for Tafamidis (IBD – 16 August 2023) - Patient Years

Indication	Region	
	EU (5EU/Mid-Level/Emerging Mkts)	Non EU (ROW)
Amyloidosis	8,269	66,179
Failure and rejection of transplanted organs and tissues	-	6,802
Cardiomyopathy	2,240	55
Total Others	2,828	0

Formulation Rx Splits are not shown as only one category was provided.

shows the cumulative exposure for Age, Gender and Dose.

Table 24. Cumulative Estimated Exposure for Tafamidis (IBD – 16 August 2023) - Patient Years

Indication	Gender		Formulation		Dose	
	17 - 65	>65	M	F	20 mg	61 mg
Amyloidosis	47,238	27,210	53,003	21,445	65,166	9,282
Failure and rejection of transplanted organs and tissues	-	6,802	-	6,802	6,802	0

Table 24. Cumulative Estimated Exposure for Tafamidis (IBD – 16 August 2023) - Patient Years

Indication	Gender		Formulation		Dose	
Cardiomyopathy	5	2,290	1,782	514	6	2,289
Total Others	0	2,828	2,576	252	507	2,320

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

Tafamidis has no sedating, anxiolytic, addictive, euphoric or stimulant properties. The potential for misuse of the product for illegal purposes is believed to be low.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the RMP version 1.0 approved on 21 July 2011 are presented in Table 25 or the list of risks in Annex 8.

Table 25. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Urinary tract infection Diarrhoea Upper abdominal pain Vaginal infection
Important potential risks	Hepatotoxicity Hypersensitivity reactions Reproductive toxicity and lactation Changes in thyroid function, particularly in pregnant women
Missing information	Safety and efficacy in elderly patients Longer term safety Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks: None

Important Potential Risk: Hepatotoxicity

Tafamidis-associated hepatic alterations in nonclinical studies 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. The observed liver findings were largely consistent with induction of adaptive responses to xenobiotic exposure in rodents and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety (see Table 3).

The acyl glucuronide metabolite of tafamidis was the sole plasma metabolite found in humans and was found in all the animal species tested in the repeat dose toxicity programme (mice, rats, and dogs). There is a theoretical risk that acyl glucuronide compounds can be associated with idiosyncratic drug reactions, particularly those associated with immune responses and hepatic toxicity. The clinical relevance of this potential toxic mechanism seems low, given the predicted lack of reactivity for tafamidis relative to other structural motifs, the low extent of metabolism, and the lack of clinical signal as of 16 August 2023 (see Table 3).

To identify potential drug-induced hepatic adverse events (AEs) the narrow scope MedDRA SMQ Drug related hepatic disorders - comprehensive search was utilised to analyse the ATTR-PN safety population. Across 5 studies (Fx-005, Fx-006, Fx1A-201, B3461010 and Fx1A-3-3/B3461023), 4 AEs were considered to be possibly related to tafamidis: increased hepatic enzyme in 2 patients, hepatomegaly in 1 patient, and hepatic lesion in 1 patient.

In study B3461028 in ATTR-CM patients, the exposure-adjusted incidence rate per 100 patient-years of patients reporting at least one hepatotoxicity-related AE (all causality) was similar for the tafamidis 20 mg (14.37; 95% confidence interval [CI]: 9.11, 21.57)], tafamidis 80 mg (12.10; 95% CI: 8.56, 16.61), and pooled tafamidis groups (12.87; 95% CI: 9.84, 16.53) and the placebo group (13.08 95% CI: 9.30, 17.89). The most commonly reported treatment- emergent AEs were gamma-glutamyl transferase increased, liver function test abnormal and blood bilirubin increased. Overall, no meaningful difference in incidence of treatment-emergent hepatic events across treatment groups was observed. The grouped distribution of abnormal liver function and liver transaminase preferred terms was similar between the placebo and tafamidis treatment groups.

Overall, although on-going pharmacovigilance of hepatic events across the tafamidis clinical programme, as well as the post-marketing experience, has not identified a clear safety signal associated with tafamidis treatment, hepatotoxicity is listed as an Important Potential Risk for tafamidis and the MAH will continue to monitor closely to further assess this potential risk.

Risk-benefit impact:

Considering that no clear evidence of hepatic adverse effects of tafamidis treatment has been observed in humans based on data as of 16 August 2023, there is no impact of such events on the risk-benefit of tafamidis. Additional data will continue to be collected to further characterise the risk and its impact on the risk benefit.

Important Potential Risk: Reproductive and Developmental Toxicity and Lactation

Based on nonclinical data (see Table 3), reproductive and developmental toxicity and lactation has been identified as an important potential risk. In an embryo-fetal developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-fetal survival, and reduction in fetal weights were observed. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation.

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

As of 31 August 2023, there were a total of 20 cases of maternal exposure in utero to tafamidis, including Maternal exposure during pregnancy (16 cases with 2 for a twin pregnancy), Maternal exposure time unspecified (2), Drug exposure before pregnancy (1) and Exposure during pregnancy (1).
These 20 cases represented 19 pregnancies (1 twin pregnancy) and 20 foetus exposure, for which pregnancy outcome was reported as follow: 13 normal newborns (including 1 low birth weight and 1 pre-term infant), 1 live birth without other information, 2 with unknown outcome, 2 medical termination (twin pregnancy), and 2 voluntary terminations.
For the medical terminations, intense vaginal haemorrhage occurred during 1st trimester in a 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.
Of the 14 live births for infants exposed to tafamidis in utero, 5 provided post-natal follow-up at 6 mths and 4 provided follow-up at 12 months (TESPO programme), reporting that the infants survived the first year of life and met their age-appropriate development milestones. No infant reported any congenital malformations/anomalies.

The Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) programme follows the progress and outcome of reported pregnancies with maternal in utero exposure 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 and developmental toxicity for tafamidis arising from findings in nonclinical developmental toxicity studies.

Overall, although ongoing pharmacovigilance of reproductive and developmental toxicity and lactation events across the tafamidis clinical programme, as well as the post-marketing experience, have not provided evidence for a safety signal associated with tafamidis treatment, Reproductive and Developmental Toxicity and Lactation is listed as an Important Potential Risk for tafamidis, and the MAH will continue to monitor closely to further assess this potential risk.

Risk-benefit impact:

Female patients who were pregnant or lactating were excluded from all clinical trials in the development programme of tafamidis. Because tafamidis administration is not recommended in pregnant women, there are currently little data on the use of tafamidis in pregnant women, and few cases of pregnancy outcome monitoring, mostly in ATTR-PN patients. While the relevance of nonclinical data to human risk is still unclear, in the limited number of human pregnancy exposures to tafamidis meglumine to date, no congenital abnormalities or impaired development have been observed. Based on this information and the age range of the ATTR-CM female patient population (46–88 years [mean 73.84 years] in Study B3461028), it is still unknown if such event would impact risk-benefit. Additional data will continue to be collected to characterise the risk and its impact on the risk-benefit.

Important Potential Risk: Changes in Thyroid Function, Particularly in Pregnant Women

In human plasma, thyroxine binding globulin (TBG) is the major thyroid hormone-binding protein. TTR binding affinity for thyroxine is intermediate to that of TBG and albumin, and TTR is only responsible for 10% to 20% of protein bound plasma thyroxine.[74] In fact, only approximately 0.5% of circulating TTR is occupied by thyroxine (T4).[75] These data would suggest that any displacement of thyroxine due to tafamidis binding would be minimal and the risk that it might impact thyroid hormone homeostasis is unlikely. This assessment is supported by the observation that perturbations in any of the binding globulins are not associated with abnormalities in thyroid hormone homeostasis but rather maintenance of the euthyroid state is observed.[74] In fact, in the presence of normal levels of TBG, wide fluctuations in TTR concentration, or its removal from serum by specific antibodies has little influence on the concentration of free T4.[76] In addition, mice lacking TTR maintain an euthyroid status despite a 50% reduction in total circulating T4 levels.[77]

Due to the theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer, a comprehensive assessment of thyroid function was performed throughout the tafamidis clinical programme. This included assessment of thyroid stimulating hormone (TSH) and total and free thyroxine (T4) in healthy volunteers and in all patient studies. Monitoring of thyroid hormone (including TSH and T4) in the tafamidis clinical trials did not demonstrate perturbations of thyroid hormone status. In Study Fx-005, changes from baseline to Month 18 in thyroid function results were similar between the treatment groups. No significant changes from baseline were observed, and mean change for tafamidis was similar to that of placebo at all time points. These data are supported by the data from Studies Fx1A-201 and Fx-006.

In Study B3461028, the observed incidence of thyroxine abnormality <0.8-times the lower limit of normal in subjects with normal or abnormal baseline values was higher in the tafamidis 80 mg group compared with the tafamidis 20 mg and placebo groups. This observation in total thyroxine values may likely be the result of reduced thyroxine binding to, or displacement from, TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor. However, no clinically meaningful shifts in free thyroxine or thyrotropin values were observed, and no corresponding signs of thyroid dysfunction were observed in

the analysis of treatment-emergent adverse events (TEAEs), suggesting that normal thyroid function was maintained.

Overall, ongoing pharmacovigilance of thyroid function events across the tafamidis clinical programme has not identified a clinically significant safety signal associated with tafamidis treatment. However, given the increased risk of thyroid dysfunction during pregnancy negatively impacting the foetus, signs and symptoms of thyroid dysfunction in pregnant women exposed to tafamidis will be sought and additional data will continue to be collected to further characterise the risk and its impact on the risk benefit. Changes in thyroid function, particularly in pregnant women is listed as an Important Potential Risk for tafamidis and the MAH will continue to monitor closely to further assess this potential risk.

Risk-benefit impact:

Considering that no clinically meaningful changes in thyroid function, particularly in pregnant women, has been observed in humans based on data to date, there appears to be no impact of such events on the risk-benefit. Additional data will continue to be collected to further characterise the risk and its impact on the risk benefit.

SVII.1.3. Missing Information in the List of Safety Concerns in the RMP

Missing Information: Patients with New York Heart Association (NYHA) Class IV

Due to the progressive nature of ATTR amyloidosis, including ATTR-CM, the administration of tafamidis to patients with NYHA Class IV disease may occur. During clinical trials for ATTR-CM, patients classified as NYHA Class IV were excluded from the pivotal Phase 3 Study B3461028. To date there is limited information on exposure to tafamidis for patients with NYHA Class IV. However, with limited data on tafamidis exposure in such patients the safety in patients with ATTR-CM NYHA Class IV is unknown. Patients with NYHA Class IV is listed as an entry in Missing Information for tafamidis and the MAH will continue to monitor closely to further assess this patient population.

Risk-benefit impact:

Considering the limited data to date on adverse effects of tafamidis treatment in patients with NYHA Class IV, the impact of such event on the risk-benefit is unknown. Additional data will continue to be assessed in this patient population and its potential impact on the risk benefit.

Missing Information: Patients with Severe Hepatic Impairment

Hepatotoxicity is listed as an Important Potential risk with details on rationale (See SVII.1.2). Pivotal clinical trials excluded patients with alanine aminotransferase and/or aspartate transaminase values more than twice the upper limit of normal (ULN) that were considered by the investigator as due to reduced liver function or active liver disease.

Caution is recommended for subjects with severe hepatic impairment since tafamidis has not been studied this population. Patients with severe hepatic impairment is listed as an entry in

Missing Information for tafamidis and the MAH will continue to monitor closely and assess the safety profile in this patient population.

Risk-benefit impact:

Considering the limited data in this population and the lack of clear evidence to date of adverse effects of tafamidis treatment in patients with severe hepatic impairment, the impact of such event on the risk-benefit is unknown. Additional data will continue to be collected to further characterise this patient population and its potential impact on the risk benefit.

Missing information: Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

The effects of tafamidis have been assessed in patients with non-Val30Met ATTR-PN in a supportive open-label trial in 21 patients and in a post-marketing observational study in 39 patients. Based on the results of these studies, the mechanism of action of tafamidis and the results on TTR stabilisation, tafamidis is expected to be beneficial in patients with stage 1 TTR amyloid polyneuropathy due to mutations other than Val30Met.

Risk-benefit impact:

Considering the paucity of data in this population and the lack of clear evidence to date of adverse effects of tafamidis treatment in patients with ATTR-PN mutations other than Val30Met, the impact of such event on the risk-benefit is unknown. Additional data will continue to be collected to further characterise this patient population and its potential impact on the risk benefit.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new important, identified, or potential risks have been identified for tafamidis since the last tafamidis EU RMP (Version 9.7, dated June 2023) was submitted.

SVII.2.1. Important Identified Risks Removed from the List of Safety Concerns

N/A.

SVII.2.2. Important Potential Risks Removed from the List of Safety Concerns

N/A.

SVII.2.3. New Missing Information Added to the List of Safety Concerns

N/A.

SVII.2.4. Missing Information Removed from the List of Safety Concerns

N/A

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks

None.

SVII.3.2. Presentation of Important Potential Risks

Table 26. Hepatotoxicity

Potential mechanisms:	The observed liver findings in rodents were largely consistent with induction of adaptive responses to xenobiotic exposure and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety (Table 3).
Evidence source and strength of evidence	Data are from nonclinical toxicity studies in rodents (Table 3). Tafamidis-associated hepatic alterations in nonclinical studies 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. The observed liver findings were largely consistent with induction of adaptive responses to xenobiotic exposure in rodents and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety. The absence of findings in clinical databases for both ATTR-PN and ATTR-CM studies support the lack of relevance to human safety.
Characterisation of the risk:	**ATTR-PN patients (Fx-005 Study/B3461020)**: Incidence proportion for hepatobiliary disorders: Placebo: 1.6%; Tafamidis 20 mg: 3% **ATTR-CM patients (Study B3461028):** Incidence proportion for hepatobiliary disorders: Placebo: 39 (22%); Tafamidis (20 mg+80 mg): 61 (23.1%) Exposure-Adjusted Incidence Rate (95% CI) for hepatobiliary disorders: Placebo: 13.08 (9.30, 17.89); Tafamidis (20 mg + 80 mg): 12.87 (9.84, 16.53)
Risk factors and risk groups:	All patients receiving tafamidis.
Preventability:	Caution is recommended for subjects with severe hepatic impairment since tafamidis has not been studied in patients with severe hepatic impairment.
Impact on the risk-benefit balance of the product:	Considering that no clear evidence of hepatic adverse effects of tafamidis treatment has been observed in humans, it is still unknown if such event would impact risk benefit. Additional data will continue to be collected to characterise the risk and its impact on the risk benefit.
Public health impact:	It is not yet possible to conclude impact on public health, as this is a potential risk that requires further characterisation.

ATTR-CM = Transthyretin amyloid cardiomyopathy; ATTR-PN = Transthyretin amyloid polyneuropathy; CI = confidence interval; n = number of subjects/patients; mg = milligram

Table 27. Reproductive and developmental toxicity and lactation

Potential mechanisms:	Unknown.
Evidence source and strength of evidence	Data are from nonclinical toxicity studies (Table 3). In an embryo-fetal developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-fetal survival, and reduction in fetal weights were observed. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation. Tafamidis is secreted in the milk of lactating rats. The relevance to humans is not clear.
Characterisation of the risk:	Frequency and Outcomes **Overall:** 19 distinct maternal in utero pregnancy exposure (20 foetuses exposure - 1 twin pregnancy) **Outcomes** (n=20): 13 normal newborns (including 1 low birth weight and 1 pre-term infant), 1 live birth without other information, 2 with unknown outcome, 2 medical termination (twin pregnancy), and 2 voluntary terminations. Of the 14 live births for infants exposed to tafamidis in utero, 5 provided post-natal follow-up at 6 months and 4 provided follow-up at 12 months (TESPO programme), reporting that the infants survived the first year of life and met their age-appropriate development milestones. No infant reported any congenital malformations/anomalies. ATTR-CM: In Study B3461028, due to a mean age of 74.5 years old (range: 46–88) for ATTR-CM patients in the Pooled tafamidis set (N=264) and a percentage of female of 8.7% for the same set, pregnancy and lactation are not expected in this population. No patient was discontinued due to pregnancy in Study B3461028. ATTR-PN: Fx-005: n=1; pregnant at Month 18 visit, tafamidis discontinued; normal pregnancy and a healthy child delivered. Fx1A-303 (B3461023): 2 subjects discontinued the study due to pregnancy. Both led to 2 live births, both without malformation; Fx-R-001 (THAOS): 1 with low birth weight (2.76 kg).
Risk factors and risk groups:	All pregnant and lactating women receiving tafamidis.
Preventability:	Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Tafamidis should be discontinued in the event of a pregnancy. Tafamidis meglumine should not be used during breastfeeding.

Table 27. Reproductive and developmental toxicity and lactation

Impact on the risk-benefit balance of the product:	Female patients who were pregnant or lactating were excluded from all clinical trials in the development programme for tafamidis. Because tafamidis administration is not recommended in pregnant women, there are currently little data on the use of tafamidis in pregnant women and few cases of pregnancy outcome monitoring, mostly in ATTR-PN patients. While the relevance to humans of the pre-clinical risks observed is still unclear, in the limited number of human pregnancy exposures to tafamidis to date, no congenital abnormalities or impaired development have been observed. Based on this information and the age range of the ATTR-CM female patient population (46–88 years [mean 73.84 years] in Study B3461028), it is still unknown if such event would impact risk-benefit. Additional data will continue to be collected to characterise the risk and its impact on the risk benefit.
Public health impact:	It is not yet possible to conclude impact on public health, as this is a potential risk and requires further characterisation.

ATTR-CM = Transthyretin amyloid cardiomyopathy; ATTR-PN = Transthyretin amyloid polyneuropathy; kg = Kilogram; N = Number; TESPO = Tafamidis Enhanced Surveillance Pregnancy Outcomes; THAOS = Transthyretin-Associated Amyloidoses Outcomes Survey

Table 28. Changes in thyroid function, particularly in pregnant women

Potential mechanisms:	The theoretical risk of thyroid function abnormalities is related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer. In human plasma, TBG is the major thyroid hormone-binding protein. TTR binding affinity for thyroxine is intermediate to that of TBG and albumin.
Evidence source and strength of evidence	Data suggest that any displacement of thyroxine due to tafamidis binding would be minimal and the risk that it might impact thyroid hormone homeostasis is unlikely. This assessment is supported by the observation that perturbations in any of the binding globulins are not associated with abnormalities in thyroid hormone homeostasis but rather maintenance of the euthyroid state is observed.[74] In fact, in the presence of normal levels of TBG, wide fluctuations in TTR concentration, or its removal from serum by specific antibodies has little influence on the concentration of free T4.[76] In addition, mice lacking TTR maintain an euthyroid status despite a 50% reduction in total circulating T4 levels.[77] Due to the theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer, a comprehensive assessment of thyroid function was performed throughout the tafamidis ATTR-PN clinical programme. This included assessment of TSH and total and free thyroxine in healthy volunteers and in all patient studies. Monitoring of thyroid hormone (including TSH and total and free thyroxine) in the tafamidis clinical trials did not demonstrate perturbations of thyroid hormone status. In placebo controlled clinical studies in ATTR-PN, changes from baseline to Month 18 in thyroid function were similar between the treatment groups. No significant changes from baseline were observed, and mean change for tafamidis was similar to that for placebo at all time points. Given that the mean changes were similar between the treatment groups, and the mean values remained within the normal range, there appears to be only a theoretical risk of tafamidis effect on thyroid function. In Study B3461028 (ATTR-CM), a small decrease from baseline in mean total thyroxine values was observed in both the tafamidis 20 mg and tafamidis 80 mg

Table 28. Changes in thyroid function, particularly in pregnant women

	groups (with greater decrease in tafamidis 80 mg) across visits; however, there were no clinically meaningful shifts in the free T4 or TSH values noted. This is also corroborated by the absence of an observed safety signal in thyroid dysfunction adverse events in the tafamidis-treated patients. This observation in total thyroxine values may likely be the result of reduced thyroxine binding to, or displacement from, TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor.
Characterisation of the risk:	Frequency: **ATTR-PN patients (Study Fx-005/B3461020):** Proportion for hypothyroidism: Placebo: 1.6%; Tafamidis (20 mg + 80 mg): 0% **ATTR-CM Patients (Study B3461028)** Any Event of Thyroid Dysfunction: Proportion: Placebo: 19 (10.7%); Tafamidis (20 mg + 80 mg): 22 (8.3%) Exposure-Adjusted Incidence Rate (95% CI): Placebo: 6.10 (3.67, 9.52); Tafamidis (20 mg + 80 mg): 4.20 (2.63, 6.36)
Risk factors and risk groups:	All patients receiving tafamidis.
Preventability:	Unknown.
Impact on the risk-benefit balance of the product:	Considering that no clear evidence of changes in thyroid function, particularly in pregnant women, has been observed in humans, it is still unknown if such event would impact risk benefit of tafamidis. Additional data will continue to be collected to characterise the risk and its impact on the risk benefit.
Public health impact:	It is not yet possible to conclude impact on public health, as this is a potential risk and requires further characterisation.

ATTR-CM = Transthyretin amyloid cardiomyopathy; ATTR-PN = Transthyretin amyloid polyneuropathy; CI = confidence interval; mg = milligrams; T4 = thyroxine; TBG = thyroxine-binding globulin; TSH = thyroid stimulating hormone; TTR = transthyretin

SVII.3.3. Presentation of the Missing Information

Table 29. Patients with NYHA Class IV (ATTR-CM indication)

Evidence source and strength of evidence	Population in need of further characterisation: Marketing Authorisation Holder-sponsored clinical trials with tafamidis have not included patients with NYHA Class IV classification, as NYHA Class IV classification was an exclusion criterion.
Anticipated risk/consequence of the missing information	The safety profile of tafamidis when using in patients with NYHA class IV is unknown.

Table 30. Patients with Severe Hepatic Impairment

Evidence source and strength of evidence	Population in need of further characterisation: The pharmacokinetics and safety of tafamidis in subjects with severely compromised liver function have not been evaluated, and thus, an increased exposure following administration of tafamidis in this patient population cannot be ruled out.
Anticipated risk/consequence of the missing information	The safety profile of tafamidis when using in patients with severe hepatic impairment is unknown.

Table 31. Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

Evidence source and strength of evidence	Population in need of further characterisation: Safety and efficacy data in patients with ATTR-PN mutations other than Val30Met
Anticipated risk/consequence of the missing information	The results collected to date indicate that tafamidis treatment in non-Val30Met patients is consistent with its profile in the treatment of ATTR amyloidosis in patients with the Val30Met genotype, however, due to the paucity of available data, the safety and efficacy in patients with ATTR-PN mutations other than Val30Met will benefit from additional characterisation.

Module SVIII. Summary of the Safety Concerns

Table 32. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity
	Reproductive and developmental toxicity and lactation
	Changes in thyroid function, particularly in pregnant women
Missing information	Patients with NYHA Class IV (ATTR-CM indication)
	Patients with severe hepatic impairment
	Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Hepatotoxicity—routine pharmacovigilance including the use of a data capture aid (DCA) for collection of data on Hepatic Events

Changes in Thyroid Function—routine pharmacovigilance including the use of a DCA for collection of data on Thyroid Dysfunction, in both the general population and in pregnant women

Reproductive developmental toxicity and lactation—routine pharmacovigilance including the standard collection of data from pregnancies (Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) Data Capture Aid)

Other forms of routine pharmacovigilance activities for safety concerns: None.

III.2. Additional Pharmacovigilance Activities

III.2.1. TESPO

Study short name and title:

Tafamidis enhanced surveillance pregnancy outcomes (TESPO).

Rationale and study objectives:

The TESPO program is intended to collect data on pregnancy outcomes in this limited population of patients who receive tafamidis during or within 1 month prior to pregnancy.

Study design:

Collection of data from pregnancy and pregnancy outcome reported through TESPO.

Study populations:

Pregnant patients with exposure to tafamidis during or within 1 month prior to pregnancy.

Milestones:

None planned unless indicated by data. Updated information on the topic will be included in PSURs.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. Ongoing and Planned Additional Pharmacovigilance Activities

Table 33. Ongoing and planned additional pharmacovigilance activities

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				
Yearly updates on any new information concerning the effects of tafamidis on disease progression and its long-term safety in non-Val30Met patients Ongoing	In order to further characterise the efficacy and safety of tafamidis in non Val30Met patients, the MAH will provide yearly updates on any new available efficacy and safety data in non-Val30Met patients	Missing information – Safety and efficacy in patients with ATTR-PN mutations other than Val30Met.	NA	Yearly, simultaneously with submission of Periodic Safety Update Reports (when applicable)
Category 3 - Required additional pharmacovigilance activities				
Tafamidis enhanced surveillance pregnancy outcomes (TESPO) Ongoing	The TESPO programme is intended to collect data on pregnancy and pregnancy outcomes in the limited population of patients who receive tafamidis during or within 1 month prior to pregnancy.	Important Potential risk- Reproductive and developmental toxicity and lactation.	Ongoing	None planned unless indicated by data.Updated information on the topic will be included in periodic safety reports

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Currently, there are no post-authorisation efficacy studies being conducted with tafamidis and none are planned.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 34. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Potential Risk	
Hepatotoxicity	Routine risk communication SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None.
Reproductive and developmental toxicity and lactation	Routine risk communication SmPC Section 4.4 SmPC section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis. Available data in animals have shown excretion of tafamidis in milk. A risk to the newborns/infants cannot be excluded. Tafamidis should not be used during breastfeeding. No impairment of fertility has been observed in nonclinical studies. Other routine risk minimisation measures beyond the Product Information: None
Changes in thyroid function, particularly in pregnant women	Routine risk communication SmPC Section 4.4 SmPC Section 4.5 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

Table 34. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Missing information	
Patients with NYHA Class IV (ATTR-CM indication)	Routine risk communication: SmPC Section: Section 4.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy. When there is a suspicion in patients presenting with specific medical history or signs of heart failure or cardiomyopathy, 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. Vyndaqel should be started as early as possible in the disease course when the clinical benefit on disease progression could be more evident. Conversely, when amyloid-related cardiac damage is more advanced, such as in NYHA Class III, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy (see Section 5.1). There are limited clinical data in patients of NYHA Class IV. Other routine risk minimisation measures beyond the Product Information: None
Patients with severe hepatic impairment	Routine risk communication: SmPC Sections: Section 4.2 Section 5.2: Routine risk minimisation activities recommending specific clinical measures to address the risk: Tafamidis has not been studied in patients with severe hepatic impairment and caution is recommended. Other routine risk minimisation measures beyond the Product Information: None
Safety and efficacy in patients with ATTR-PN mutations other than Val30Met	Routine risk communication Vyndaqel 20 mg SmPC Sections: Routine risk minimisation activities recommending specific clinical measures to address the risk: Although data are limited, (one open-label study in 21 patients and a post-marketing observational study in 39 patients), taking into account the mechanism of action of tafamidis and the results on TTR stabilisation, Vyndaqel is expected to be beneficial in patients with stage 1 ATTR-PN due to mutations other than Val30Met.

Table 34. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation activities: Healthcare Professional (HCP) Guide (formally known as the HCP education leaflet)

Objectives:

The objective of the aRMM is to optimise the safe and effective use of tafamidis and will be achieved as follows:

For the Important Potential Risk of "Reproductive and developmental toxicity and lactation"

- Highlight this important potential risk (tafamidis is not recommended during pregnancy, lactation, or breastfeeding), encourage patient education around appropriate precautions (need for effective contraception while on tafamidis) and encourage prescriber's reporting of pregnancies.

- Advise patients to contact their prescriber about adverse events and physicians/pharmacists should report suspected adverse reactions related to Vyndaqel.

- Advise female patients to inform their doctor immediately in case of exposure to tafamidis during (or within 1 month prior to) pregnancy for physician’s reporting and assessment.

- Provide a description of Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) for reporting of pregnancy, pregnancy outcome up to 1-year follow-up for infants.

For the Missing Information of "Patients with NYHA Class IV (ATTR-CM indication)"

- Specify the clinical criteria to be verified for the diagnosis of ATTR-CM patients and highlight the section of the SmPC where this is mentioned.

Target audience and planned distribution path:

The 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 marketed for ATTR-CM.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities to identify new safety signals.

V.3. Summary of Risk Minimisation Measures

Table 35. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Use of DCA for Hepatic Events Additional pharmacovigilance activities: 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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Use of a DCA for Thyroid Dysfunction in both the general population and in pregnant women. Additional pharmacovigilance activities: 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Standard collection of data from pregnancies. Additional pharmacovigilance activities: Tafamidis enhanced surveillance pregnancy outcomes (TESPO) data capture aid
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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.
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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Table 35. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Yearly updates on any new information concerning the effects of tafamidis on disease progression and its long-term safety in non Val30Met patients.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Vyndaqel 20 mg (tafamidis meglumine) and Vyndaqel 61 mg (tafamidis)

This RMP details important risks of Vyndaqel, how these risks can be minimised, and how more information will be obtained about Vyndaqel's risks and uncertainties (missing information).

Vyndaqel's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vyndaqel should be used.

This summary of the RMP for Vyndaqel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vyndaqel's RMP.

I. The Medicine and What It Is Used For

Vyndaqel is authorised for the treatment of transthyretin amyloidosis (ATTR) in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment and is proposed for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (see SmPC for the full indication). It contains tafamidis meglumine or tafamidis free acid as the active substance and it is given by oral route of administration.

Further information about the evaluation of Vyndaqel’s benefits can be found in Vyndaqel’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/documents/overview/vyndaqel-epar-summary-public_en.pdf

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Vyndaqel, together with measures to minimise such risks and the proposed studies for learning more about Vyndaqel's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

Important advice on the medicine’s packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Vyndaqel is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Vyndaqel are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vyndaqel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 36. List of important risks and missing information

Important identified risks	None
Important potential risks	Hepatotoxicity Reproductive and developmental toxicity and lactation Changes in thyroid function, particularly in pregnant women
Missing information	Patients with NYHA Class IV (ATTR-CM indication) Patients with severe hepatic impairment Safety and efficacy in patients with ATTR-PN mutations other than Val30Met

II.B. Summary of Important Risks

Table 37. Important Potential Risks

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Data are from nonclinical toxicity studies in rodents. Tafamidis-associated hepatic alterations in nonclinical studies 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. The observed liver findings were largely consistent with induction of adaptive responses to xenobiotic exposure in rodents and/or exacerbation of normal aging changes and, consequently, are not relevant to human safety. The absence of findings in clinical databases for both ATTR-PN and ATTR-CM studies support the lack of relevance to human safety.

Table 37. Important Potential Risks

Risk factors and risk groups	All patients receiving tafamidis.
Risk Minimisation Measures	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.
Additional Pharmacovigilance Activities	None.
Important Potential Risk: Reproductive and developmental toxicity and lactation	
Evidence for linking the risk to the medicine	Data are from nonclinical toxicity studies. In an embryo-fetal developmental toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, reduced embryo-fetal survival, and reduction in fetal weights were observed. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation. Tafamidis is secreted in the milk of lactating rats. The relevance to humans is unknown.
Risk factors and risk groups	All pregnant and lactating women receiving tafamidis.
Risk Minimisation Measures	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
Additional Pharmacovigilance Activities	TESPO programme.
Important Potential Risk: Changes in thyroid function, particularly in pregnant women	
Evidence for linking the risk to the medicine	Data suggest that any displacement of thyroxine due to tafamidis binding would be minimal and the risk that it might impact thyroid hormone homeostasis is unlikely. This assessment is supported by the observation that perturbations in any of the binding globulins are not associated with abnormalities in thyroid hormone homeostasis but rather maintenance of the euthyroid state is observed.[41] In fact, in the presence of normal levels of TBG, wide fluctuations in TTR concentration, or its removal from serum by specific antibodies has little influence on the concentration of free T4.[43] In addition, mice lacking TTR maintain an euthyroid status despite a 50% reduction in total circulating T4 levels.[44] Due to the theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer, a comprehensive assessment of thyroid function was performed throughout the tafamidis ATTR-PN clinical programme. This included assessment of TSH and total and free thyroxine in healthy volunteers and in all patient studies. Monitoring of thyroid hormone (including TSH and total and free thyroxine) in the tafamidis clinical trials did not demonstrate perturbations of thyroid hormone status. In placebo controlled clinical studies in ATTR-PN, changes from baseline to Month 18 in thyroid function were similar between the treatment groups. No significant changes from baseline were observed, and mean change for tafamidis was similar to that for placebo at all time points. Given that the mean changes were similar between the treatment groups, and the mean values remained within

Table 37. Important Potential Risks

	the normal range, there appears to be only a theoretical risk of tafamidis effect on thyroid function. In Study B3461028 (ATTR-CM), a small 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) across visits; however, there were no clinically meaningful shifts in the free T4 or TSH values noted. This is also corroborated by the absence of an observed safety signal in thyroid dysfunction adverse events in the tafamidis-treated patients. This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from TTR due to the high binding affinity tafamidis has to the TTR thyroxine receptor.
Risk factors and risk groups	All patients receiving tafamidis.
Risk Minimisation Measures	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.
Additional Pharmacovigilance Activities	None.

Table 38. Missing Information

Missing information: Patients with NYHA Class IV (ATTR-CM indication)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Additional risk minimisation measures: HCP Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections: Section 4.2 Posology and method of administration Section 5.2: Pharmacokinetic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Safety and efficacy in patients with ATTR-PN mutations other than Val30Met	

Table 38. Missing Information

Risk minimisation measures	Routine risk minimisation measures: Vyndaqel 20 mg SmPC Sections: 5.1, Pharmacodynamic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Yearly updates on any new information concerning the effects of tafamidis on disease progression and its long-term safety in non-Val30Met patients.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

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): Yearly updates on any new information concerning the effects of tafamidis on disease progression and its long-term safety in non-Val30Met patients.

II.C.2. Other Studies in Post-Authorisation Development Plan

Category 3 (required additional pharmacovigilance activities): 1 ongoing

Study short name: Tafamidis enhanced surveillance pregnancy outcomes (TESPO)

Purpose of the study: The TESPO program is intended to improve data collection on pregnancy and pregnancy outcomes in this limited population of patients who receive tafamidis during or within a month prior to pregnancy.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES

[1] Blake CC, Geisow MJ, Oatley SJ, Rerat B, Rerat C. Structure of prealbumin: secondary, tertiary, and quaternary interactions determined by Fourier refinement at 1.8 A. J Mol Biol. 1978; 121: 339-356.

[2] Monaco HL, Rizzi M, Coda A. structure of a complex of two plasma proteins: transthyretin and retinol-binding protein. Science 1995;268: 1039-1041.

[3] Kittleson et al J Am Coll Cardiol. 2023 Mar, 81 (11) 1076–1126.

[4] Connelly S, Choi S, Johnson SM, et al. Structure based design of kinetic stabilizers that ameliorate the transthyretin amyloidoses. Curr Opin Struct Biol 2010; 20(1):54-62.

[5] Klabunde T, Petrassi HM, Oza VB, et al. Rational design of potent human transthyretin amyloid disease inhibitors. Nat Struct Biol 2000; 7(4):312-21.

[6] Johnson SM, Wiseman RL, Sekijima Y, et al. Native state kinetic stabilization as a strategy to ameliorate protein misfolding diseases: A focus on the transthyretin amyloidoses. Acc Chem Res 2005; 38(12):911-21.

[7] Sekijima Y, Kelly JW, Ikeda S. Pathogenesis and therapeutic strategies to ameliorate the transthyretin amyloidoses. Curr Pharm Des 2008; 14(30):3219-30.

[8] Benson MD. Amyloidosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Diseases Vol. 4. New York, NY: McGraw-Hill; 2001:5345-78.

[9] Ando Y, Nakamura M,Araki S. Transthyretin-related familial amyloidotic polyneuropathy. Arch Neurol 2005;62(7):1057-62.

[10] Coutinho P, Martins da Silva A, Lopes Lima J, et al. Forty years of experience with type I amyloid neuropathy. Review of 483 cases. In: Glenner GG, Pinho e Costa P, Falcao de Freitas A, eds. Amyloid and Amyloidosis. Amsterdam, Netherlands: Excerpta Medica; 1980:88-98.

[11] Herlenius G, Wilczek HE, Larsson M, et al. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation 2004;77(1):64-71.

[12] Lewis WD, Skinner M, Simms RW, et al. Orthotopic liver transplantation for familial amyloidotic polyneuropathy. Clin Transplant 1994;8:107-10.

[13] Holmgren G, Steen L, Ekstedt J, et al. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). Clin Genet 1991;40(3):242-6.

[14] Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain 2000;123(Pt 7):1495-504.

[15] Tashima K, Ando Y, Terazaki H, et al. Outcome of liver transplantation for transthyretin amyloidosis: follow-up of Japanese familial amyloidotic polyneuropathy patients. J Neurol Sci 1999;171(1):19-23.

[16] Schmidt HH, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, Stewart M, Fallet S, Amass L. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2018 May;57(5):829-837

[17] Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, Coelho T; European Network for TTR-FAP (ATTReuNET). Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016 Feb;29 Suppl 1:S3-S13

[18] Lobato L. Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). J Nephrol 2003;16(3):438-42.

[19] Kato-Motozaki Y, Ono K, Shima K, et al. Epidemiology of familial amyloid polyneuropathy in Japan: Identification of a novel endemic focus. J Neurol Sci 2008;270(1-2):133-140.

[20] Cruz MW. Regional differences and similarities of familial amyloidotic polyneuropathy (FAP) presentation in Brazil. Amyloid. 2012;19 Suppl 1:65-67. doi:10.3109/13506129.2012.673183

[21] Cruz MW, Pinto MV, Pinto LF, et al. Baseline disease characteristics in Brazilian patients enrolled in Transthyretin Amyloidosis Outcome Survey (THAOS). Arq Neuropsiquiatr. 2019;77(2):96-100.

[22] Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7(7):398-408.

[23] Augustin S, Llige D, Andreu A, et al. Familial amyloidosis in a large Spanish kindred resulting from a D38V mutation in the transthyretin gene. Eur J Clin Invest 2007;37(8):673-8.

[24] Inês M, Coelho T, Conceição I, Duarte-Ramos F, de Carvalho M, Costa J. Epidemiology of Transthyretin Familial Amyloid Polyneuropathy in Portugal: A Nationwide Study. Neuroepidemiology. 2018;51(3-4):177-182.

[25] Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm [published correction appears in Orphanet J Rare Dis. 2019 May 21;14(1):111]. Orphanet J Rare Dis. 2018;13(1):6. Published 2018 Jan 17.

[26] Plante-Bordeneuve V, Lalu T, Misrahi M, et al. Genotypic-phenotypic variations in a series of 65 patients with familial amyloid polyneuropathy. Neurology 1998;51(3):708-14.

[27] Plante-Bordeneuve V, Carayol J, Ferreira A, et al. Genetic study of transthyretin amyloid neuropathies: carrier risks among French and Portuguese families. J Med Genet 2003;40(11):e120.

[28] Di Iorio G, Sanges G, Cerracchio A, et al. Familial amyloidotic polyneuropathy: description of an Italian kindred. Ital J Neurol Sci 1993;14(4):303-9.

[29] Durmus-Tekce H, Matur Z, Mert Atmaca M, et al. Genotypic and phenotypic presentation of transthyretin-related familial amyloid polyneuropathy (TTRFAP) in Turkey. Neuromuscul Disord 2016;26:441–446

[30] Kim DH, Zeldenrust SR, Low PA, et al. Quantitative sensation and autonomic test abnormalities in transthyretin amyloidosis polyneuropathy. Muscle Nerve 2009;40(3):363-70.

[31] Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. Mayo Clin Proc 1992;67(5):428-40.

[32] Tashima K, Suhr OB, Ando Y, et al. Gastrointestinal dysfunction in familial amyloidotic polyneuropathy (ATTR Val30Met)--comparison of Swedish and Japanese patients. Amyloid 1999;6(2):124-9.

[33] Ikeda S. Clinical picture and outcome of transthyretin-related familial amyloid polyneuropathy (FAP) in Japanese patients. Clin Chem Lab Med 2002;40(12):1257-61.

[34] Lee YJ, Oh J, Hwang SK, et al. Extremely Early Onset Transthyretin Familial Amyloid Polyneuropathy with a Leu55Pro Mutation: A Pediatric Case Report and Literature Review. Neuropediatrics. 2019 Oct;50(5):322-326

[35] Sousa, A, Coelho T, Barros J, et al. Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Povoa do Varzim and Vila do Conde (north of Portugal). Am J Med Genet 1995;60(6):512-21

[36] Cruz MW. Regional differences and similarities of familial amyloidotic polyneuropathy (FAP) presentation in Brazil. Amyloid. 2012;19 Suppl 1:65-67.

[37] Coelho T, Inês M, Conceição I, Soares M, de Carvalho M, Costa J. Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy. Neurology. 2018;91(21):e1999-e2009.

[38] Lauppe R, Liseth Hansen J, Fornwall A, et al. Prevalence, characteristics, and mortality of patients with transthyretin amyloid cardiomyopathy in the Nordic countries. ESC Heart Fail. 2022;9(4):2528-2537.

[39] Winburn I, Ishii T, Sumikawa T, Togo K, Yasunaga H. Estimating the Prevalence of Transthyretin Amyloid Cardiomyopathy in a Large In-Hospital Database in Japan. Cardiol Ther. 2019;8(2):297-316.

[40] Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016; 133(24):2404-12.

[41] Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol 2016; 1(8):880-9.

[42] AbouEzzeddine OF, Davies DR, Scott CG, et al. Prevalence of Transthyretin Amyloid Cardiomyopathy in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol. 2021 Nov 1;6(11):1267-1274.

[43] Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015; 36(38):2585-94.

[44] Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017; 38(38):2879-87.

[45] Damy T, Costes B, Hagege AA, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J 2016; 37(23):1826-34.

[46] Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail. 2019;7(8):709–16.

[47] Yamada T, Takashio S, Arima Y, et al. Clinical characteristics and natural history of wild-type transthyretin amyloid cardiomyopathy in Japan. ESC Heart Fail. 2020;7(5):2829-2837.

[48] Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 11;73(22):2872-2891.

[49] Buxbaum J, Jacobson D, Tagoe C, et al. Transthyretin V122I in African Americans with congestive heart failure. J Am Coll Cardiol, 2006; 47(8):1724-5

[50] Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med 2015; 372(1):21-9.

[51] Parcha V, Malla G, Irvin MR, et al. Association of Transthyretin Val122Ile Variant With Incident Heart Failure Among Black Individuals. JAMA. 2022 Apr 12;327(14):1368-1378.

[52] M.S. Maurer, M. Hanna, M. Grogan, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol, 68 (2016), pp. 161-172

[53] Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. NEJM 1997; 336:466-73.

[54] Saraiva MJ. Transthyretin mutations in health and disease. Hum Mutat 1995; 5(3):191-6.

[55] Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J 2012;164(2):222-228

[56] Falk RH. Cardiac Amyloidosis: a treatable disease, often overlooked. Circulation 2011; 124(9):1079 85.

[57] Lewis WD, Skinner M, Simms RW et al. Orthotopic liver transplantation for familial amyloidotic polyneuropathy. Clin Transplant 1994; 8(2 Pt 1):107-10.

[58] Holmgren G, Ericzon BG, Groth CG et al. Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. Lancet 1993; 341(8853):1113-6.

[59] Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):.

[60] Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012;126(10):1286-300.

[61] Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol 2016;68(2):161-72.

[62] Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018;28(1):10-21.

[63] Amacher DE, Schomaker SJ, Burkhardt JE. The relationship among microsomal enzyme induction, liver weight and histological change in rat toxicology studies. Food Chem Toxicol 1998;36:831 9.

[64] Cattley RC, Cullen JM. Liver and gall bladder. In: Haschek WM, Rousseaux CG, Wallig MA, et al, editors. Haschek and Rousseaux's handbook of toxicologic pathology. 3rd ed. Elsevier 2013;1509-66.

[65] Greaves P. Histopathology of preclinical toxicity studies. Liver and pancreas. 4th ed. Chapter 9. Elsevier 2013;433-535.

[66] Hall AP, Elcombe CR, Foster JR, et al. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd international ESTP expert workshop. Toxicol Pathol 2012;40:971 94.

[67] Regan SL, Maggs JL, Hammond TG, et al. Acyl glucuronides: the good, the bad and the ugly. Biopharm Drug Dispos 2010;31(7):367–95.

[68] Baba A and Yoshioka T. Structure-activity relationships for degradation reaction of 1-β-O-acyl glucuronides: kinetic description and prediction of intrinsic electrophilic reactivity under physiological conditions. Chem Res Toxicol 2009;22(1):158-72.

[69] Committee for Human Medicinal Products [CHMP]. EMA Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012: 59 pages.

[70] Suhr O, Danielsson A, Holmgren G, et al. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. J Intern Med 1994;235(5):479-85.

[71] Suhr OB, Ericzon BG, Friman S. Long-term follow-up of survival of liver transplant recipients with familial amyloid polyneuropathy (Portuguese type). Liver Transpl 2002;8(9):787-94.

[72] Suhr OB, Holmgren G, Steen L et al. Liver transplantation in familial amyloidotic polyneuropathy. Follow-up of the first 20 Swedish patients. Transplantation 1995;15;60(9):933-8.

[73] Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain 2000;123(7):1495-504.

[74] Palha JA. Transthyretin as a thyroid hormone carrier: function revisited. Clin Chem Lab Med. 2002;40:1292-300.

[75] Refetoff S. Thyroid Hormone Serum Transport Proteins. In: L. J. DeGroot, P. R. Larsen and G. Henneman, eds. The Thyroid and its Diseases. 6 ed. New York: Churchill Linvingstone; 1996

[76] Woeber KA and Ingbar SH. The contribution of thyroxine-binding prealbumin to the binding of thyroxine in human serum, as assessed by immunoadsorption. J Clin Invest. 1968;47:1710-21.

[77] Palha JA, Episkopou V, Maeda S, Shimada K, Gottesman ME and Saraiva MJ. Thyroid hormone metabolism in a transthyretin-null mouse strain. J Biol Chem. 1994;269:33135-9.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO)

Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) 6-Month and 12-Month Infant Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

TIMEPOINT OF INFANT OUTCOME ASSESSMENT *(Check one):*

☐ **6-MONTH** ☐ **12-MONTH**

1. Source of information provided on this form: *(Check one):*

☐ Pediatrician ☐ Mother ☐ Other *(please specify):*

2. Describe length of maternal exposure to tafamidis (both before and during pregnancy):

_____

3. Was mother taking tafamidis while breastfeeding?

☐ No ☐ Yes *(please also answer the following):*

Were there any interruptions?

_____

At what age was infant exposed to tafamidis via breast milk and for how long? _____

Is breastfeeding a supplementary or the sole source of infant's nutrition (what % of infant's nutrition is via breastmilk)? _____

6. Has the child met age-appropriate development milestones?

☐ Yes ☐ No *(If no, please describe developmental abnormalities):*

Details:

7. Does the child have congenital malformations?

☐ No ☐ Yes *(If yes please describe malformation):*

Details:

If Yes, was congenital anomaly confirmed by a physician?

☐ No ☐ Yes ☐ Unknown

Details:

8. Was chromosomal testing performed?

☐ No

☐ Unknown

☐ Yes (*please describe child's chromosomal abnormalities if present):*

Details:

9. Please describe all of child's hospitalizations, major illnesses and regular use of medications

Details:

4. Child's Birth date: *(dd/Mmm/yyyy)*: _____		**10. Are child's vaccinations up to date?** ☐ Yes ☐ Unknown ☐ No *(what is missing?):* *Details:*
5. Did the child survive the first ☐ 6 months / ☐ 12 months of life? ☐ Yes ☐ No *(If no, please provide cause of death and copy of death certificate if available):* *Details:*		

Hepatic Events Data Capture Aid

Hepatic Events Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event
☐ Recurrence *(Please specify details of the prior events)*
☐ Exacerbation of existing condition *(please provide details)*

Details:

2. Please provide: name, e-mail address, postal address, and telephone number of any specialist to whom the patient was referred for further evaluation of the reported adverse event(s) *(if applicable based on local privacy regulations):*

3. Please mark whether the patient experienced any of the following signs / symptoms:

☐ Rash ☐ Pruritus ☐ Purpura
☐ Fever ☐ Joint Pain ☐ Abdominal distension
☐ Abdominal Pain ☐ Nausea ☐ Vomiting
☐ Coma ☐ Ascites ☐ Asthenia
☐ Asterixis / "Flapping" ☐ Jaundice ☐ Hepatomegaly
☐ Splenomegaly ☐ Weight gain *(please specify)*_____
☐ Hepatic encephalopathy
☐ Sepsis *(if yes, describe time to onset and course of the event [e.g., progression and outcome])*_____
☐ Multi-organ failure *(if yes, include time to onset and the course [e.g., progression and outcome])*_____
☐ Other signs / symptoms *(including those related to infections, please specify)* _____

4. Was hepatic function test monitoring (e.g., AST, ALT, Bilirubin) done at the following times?

- **Routine LFTs <u>in year prior to start of drug</u>:**
  ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **Baseline at start of therapy** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

Details:

- **During therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

- **After therapy:** ☐ Unknown ☐ No ☐ Yes

If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

Details:

5. Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide details - specify the products generic names, dates off administration, and dosage)*

- ☐ Antibiotics
- ☐ Anti-arrhythmic drugs
- ☐ ACE inhibitors
- ☐ Potassium supplements
- ☐ Protease inhibitors
- ☐ Retroviral agents
- ☐ Anticoagulants
- ☐ Diuretics
- ☐ Beta blockers
- ☐ Angiotensin II receptor antagonists
- ☐ Potassium-sparing diuretics
- ☐ PDE5 inhibitors
- ☐ Vitamin K antagonists
- ☐ Cyclosporin A
- ☐ Oral contraceptives
- ☐ Dietary supplements
- ☐ Over-the-counter drugs
- ☐ Herbal preparations
- ☐ Recreational drugs (e.g., cocaine, crack cocaine, heroin, methamphetamines)
- ☐ Cytotoxic chemotherapy
- ☐ Disease modifying drugs (e.g. DMARD medications for the treatment of rheumatoid arthritis)
- ☐ Other heart or blood pressure medications
- ☐ Products for the treatment of pulmonary arterial hypertension
- ☐ Other *(please specify)* _____
- ☐ None

Details:

6. Please mark whether the patient had prior to start of therapy any of the following: *(Please provide details and indicate whether ongoing condition or whether occurred in the past)*

- ☐ Hepatic dysfunction
- ☐ Hepatobiliary disease or dysfunction
- ☐ Elevated liver function tests
- ☐ Elevated bilirubin
- ☐ Jaundice
- ☐ Cirrhosis
- ☐ Fatty liver
- ☐ Pancreatitis
- ☐ Gallstones
- ☐ Gall bladder disease
- ☐ Bile duct obstruction
- ☐ Viral hepatitis
- ☐ Congenital heart disease
- ☐ Drug-induced liver toxicity *(please specify drug)* _____
- ☐ Recent travel to other countries *(please specify)*
- ☐ Other *(please specify)* _____
- ☐ Alcohol use *(If checked, complete question 8)*

Details:

- ☐ Parasitic diseases
- ☐ Mycobacterium Avium Complex infection
- ☐ Other non-viral suspected liver infections
- ☐ Cytomegalovirus infection
- ☐ Ischemic hepatitis
- ☐ Cystic fibrosis
- ☐ Granulomatosis
- ☐ Sickle cell anemia
- ☐ Connective tissue disease

- ☐ Lactic acidosis syndrome
- ☐ Blood product transfusions
- ☐ Renal impairment
- ☐ Gilbert's disease
- ☐ Metabolic disease
- ☐ Diabetes mellitus (Type I or II)
- ☐ Heart failure
- ☐ Hypertension
- ☐ Hypertriglyceridemia
- ☐ Portal hypertension
- ☐ Veno-occlusive disease
- ☐ Atherosclerotic / vascular disease
- ☐ Transplant
- ☐ Contact with jaundiced patient
- ☐ Epstein–Barr virus infection
- ☐ Substance abuse/Drug abuse (e.g., recreational/illicit drug use)
- ☐ Alternative medication use (e.g., herbal supplements and vitamins)
- ☐ None

- ☐ Valvular heart disease
- ☐ Primary malignancy
- ☐ Liver metastases
- ☐ Hepatoma
- ☐ Auto-immune disorder
- ☐ Immune reconstitution disease
- ☐ HIV infection
- ☐ Sepsis
- ☐ Drug toxicity *(please specify)* _____
- ☐ Vitamin deficiency *(please specify)* _____

7. Did the patient have a <u>family history</u> of liver disease? *(i.e., genetic conditions)* ☐ Unknown ☐ No ☐ Yes *(please provide details)* *Details:*		**8. If "Alcohol use" checked above, please answer the following:** How often does the patient drink beverages containing alcohol? _____*(e.g., monthly, 2-4 times a week, more than 5 times a week, etc)* How many drinks on a typical day when patient is drinking?: _____ *(e.g., less than 1 drink, 2 or 3 drinks, more than 3 drinks, etc)* Please specify the type/brand of alcohol patient typically drinks: _____ *(e.g., beer)* If this drinking history is more than one year, please specify duration: _____

9. Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.

Laboratory Test / Procedure	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ AST			
☐ ALT			
☐ GGT			
☐ Total bilirubin			
☐ Conjugated bilirubin			
☐ Total protein			
☐ Albumin			
☐ Prothrombin time (PT)			
☐ Partial thromboplastin time (PTT)			
☐ International normalized ratio (INR)			
☐ Clotting time			
☐ Alkaline phosphatase			
☐ Hepatitis A serology			
☐ Hepatitis B serology			
☐ Hepatitis C serology			
☐ Cytomegalovirus (CMV) serology			
☐ Epstein Barr serology			
☐ Other serology			
☐ Eosinophil count			
☐ Amylase			
☐ Lipase			
☐ Other pancreatic enzymes tests			
☐ Serum or plasma concentrations for any concomitant drugs			
☐ Liver ultrasound			
☐ Liver biopsy			
☐ Abdominal X-ray			
☐ Abdominal CT			

☐ Abdominal endoscopic retrograde cholangiopancreatography (ERCP)			
☐ Serum ceruloplasmin			
☐ Serum copper			
☐ Serum alpha 1-antitrypsin			
☐ Serum alpha-fetoprotein			
☐ Serum ammonia			
☐ Other relevant lab data *(please specify)*			

Thyroid Dysfunction Data Capture Aid

Thyroid Dysfunction Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event
☐ Recurrence *(please provide details on previous events)*
☐ Exacerbation of underlying condition *(please provide details)*

2. Please indicate if there is a personal or family history of thyroid disease.

Personal

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Family

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

3. Please provide name and contact information of the HCP specialist to whom patient was referred to for further evaluation

Details:

4. Please identify any diagnostic tests and provide results, along with dates performed and reference ranges, if applicable.

☐ Thyroid scan ☐ Thyroid ultrasound
☐ Thyroid biopsy (FNA or ultrasound-guided)
☐ CT/MRI of neck ☐ Other *(specify)*
☐ None ☐ Don't know

6. Please mark whether the patient experienced any of the following clinical signs/symptoms:

☐ Fatigue, lethargy
☐ Weight gain/loss
☐ Somnolence
☐ Nonpitting edema (myxedema)
☐ Myalgia
☐ Constipation
☐ Palpitations, sinus tachycardia
☐ Atrial fibrillation
☐ Anxiety, irritability
☐ Thyroid mass/nodule
☐ Thyroid swelling/pain
☐ Excessive sweating
☐ Cold intolerance
☐ Hoarse voice
☐ Hair loss
☐ Dry hair/skin
☐ Change in deep tendon reflexes
☐ Frequent bowel movements

Details:

7. Were thyroid function tests (TSH, serum T4, T3, TBG) done at the following times? Please provide reference ranges, dates that the tests were performed and units of measurement.

Routine thyroid function tests in year prior to start of drug?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Baseline at start of therapy?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

5. Please indicate medication or intervention given to treat the reported event involving thyroid dysfunction. ☐ Steroids ☐ Methimazole ☐ Levothyroxine (T4) ☐ Propylthiouracil (PTU) ☐ Radiation/ radioiodine ☐ Surgery ☐ None ☐ Don't know ☐ Others (specify)		**During therapy?** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details* *Details:* **After therapy?** ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details* *Details:*

1. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Key messages of the additional risk minimisation measures

Prior to the launch of Vyndaqel (tafamidis) in each Member State, the Marketing Authorisation Holder (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/breastfeeding 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/breastfeeding for physicians's 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.

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: