22 September 2011
EMA/729083/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyndaqel

tafamidis meglumine

Procedure No.: EMEA/H/C/002294

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransaminase
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
AV	atrioventricular
BUN	blood urea nitrogen
Ca	calcium
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FAP	familial amyloid polyneuropathy
FAPWTR	Familial Amyloidotic Polyneuropathy World Transplant Registry
FDA	Food and Drug Administration
FOI	fraction of initial
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRDB	heart rate response to deep breathing
ICH	International Conference on Harmonisation
ID	identification
ITT	intent-to-treat
IVRS	interactive voice response system
ITTSA	FoldRx Pharmaceuticals, Inc. immunoturbimetric stabilization assay
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	kilogram
LOCF	last observation carried forward
LL	lower limb
LS	Mean Least squares mean
mBMI	modified body mass index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
NCS	nerve conduction studies
NIS-LL	Neuropathy Impairment Score – Lower Limb
NOAEL	No observed adverse event level
NOEL	No observed effect level
Norfolk QOL-DN	Norfolk Quality of Life – Diabetic Neuropathy
NSAID	non-steroidal anti-inflammatory drug
NT-pro-BNP	N-terminal prohormone brain natriuretic peCo-Rapide
NYHA	New York Heart Association
OTC	over-the-counter
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic(s)
PT	prothrombin time
QD	once a day

QOL	quality of life
QOL-DN	Quality of life – diabetic neuropathy
QST	quantitative sensory testing
RBC	red blood cell count
RPB	Retinal protein binding
SAE	serious adverse event
SAS	statistical analysis system
SD	standard deviation
SOC	system organ class
T4	total thyroxine
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
TQOL	Total Quality of Life
TSH	thyroid-stimulating hormone
TTR	transthyretin
ULN	upper limit of normal
UTI	urinary tract infection
V30M	valine replaced by methionine at position 30
VDT	vibration detection threshold
WBC	white blood cell count
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Specialty UK Limited submitted on 28 July 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vyndaqel, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP during its meeting on 15-18 February 2010.

Vyndaqel was designated as an orphan medicinal product EU/3/06/401 on 28 August 2006. Vyndaqel was designated as an orphan medicinal product in the following indication: Treatment of familial amyloid polyneuropathy. The calculated prevalence of this condition was less than 0.1 per 10,000 EU population.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Vyndaqel as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find Medicine/Human medicines/Rare disease designations.

The applicant applied for the following indication: oral treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/147/2010 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance tafamidis contained in the above medicinal product to be considered as a new active substance in itself.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 26 June 2008. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following country: United States of America.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Philippe Lechat**

Co-Rapporteur: **Helder Mota-Filipe**

- The application was received by the EMA on 28 July 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 November 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 November 2010.
- During the meeting on 13-16 December 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 Decembert 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 6 May 2011.
- During the CHMP meeting on 16-19 May 2011, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of List of Outstanding Issues to all CHMP members on 5 July 2011.
- During the meeting on 18-21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Vyndaqel on 21 July 2011.

2. Scientific discussion

2.1. Introduction

Familial transthyretin amyloidosis (ATTR) is characterised by a slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy as well as cardiomyopathy, nephropathy, vitreous

opacities and CNS amyloidosis. The onset of the disease is usually in the third to fifth decade. ATTR, the most frequently inherited amyloidosis, is caused by an accumulation of insoluble fibrillar proteins (amyloid) in the tissues. Typically, sensory neuropathy starts in the lower extremities and is followed by motor neuropathy within a few years. Autonomic neuropathy may occur as the first clinical symptom of the disease. The symptoms of autonomic dysfunction include orthostatic hypotension, constipation alternating with diarrhoea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis and urinary retention or incontinence.

The TTR protein normally circulates in serum or plasma as a soluble protein with a tetrameric structure. Pathogenic mutations in the TTR gene cause conformational change in the TTR protein molecule disrupting the stability of the TTR tetramer, which is then more easily dissociated into pro-amyloidogenic monomers. The most frequent pathogenic mutation is VAL30MET (V30M) and it is the one most often detected in Portuguese and Swedish families.

The prevalence of this disease is extremely rare; in Europe, the overall population of patients with ATTR-PN is estimated at approximately 2,700 to 3,500, which would correspond to a worldwide prevalence of 5,000 to 10,000 patients.

To date, the only effective therapy for the neuropathy of familial TTR amyloidosis is the orthotopic liver transplantation (OLTX), which removes the main production site of the amyloidogenic protein. Successful OTLX results in rapid disappearance of variant TTR protein from the serum and thus helps disrupt progression of peripheral and/or autonomic neuropathy. Of the more than 1,500 liver transplants reported to the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) since 1995, more than 80% were performed in V30M ATTR-PN patients confirming the worldwide prevalence of this mutation. Limited clinical follow-up studies showed that the neuropathy appears to stabilize following transplantation in many patients. In the cases reported to the FAPWTR for which 5- and 10- year data were available, the five- and ten-year survival rates for the ATTR-PN patients undergoing liver transplantation were 77% and 71%, respectively. However, the first-year post-transplant mortality rate is approximately 10%.

The effect of liver transplantation in the cardiac involvement of the neuropathic form is less clear, with a persistence of cardiac disease progression in most cases.

OLTX is not effective in the non-neuropathic forms of familial TTR amyloidosis (e.g. cardiac amyloidosis).

Tafamidis is a compound that binds non-cooperatively to the two transthyretin (TTR) binding sites and was developed as an oral specific stabiliser of TTR tetramer. It is intended for the oral treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy. Tafamidis is a stabilizer of both tetrameric wild-type TTR and of amyloidogenic variants of TTR. By binding to the native tetrameric form of TTR, tafamidis inhibits tetramer dissociation, the rate limiting step in the formation of TTR amyloid. By inhibiting TTR amyloid formation, this novel class of TTR stabilizer drug has a potential to disrupt the progression of ATTR. The specificity of the binding to TTR limits tafamidis to the treatment of TTR amyloidosis only, with no activity anticipated for other types of amyloidosis.

2.2. Quality aspects

2.2.1. Introduction

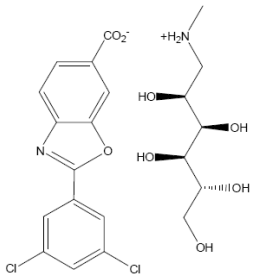
Vyndaqel is presented in an immediate-release dosage form consisting in a soft gelatin capsule containing 20 mg of micronized tafamidis meglumine. Other ingredients are:

Capsule shell: gelatin, glycerine, sorbitol liquid (E420), titanium dioxide (E171), purified water
Capsule contents: polyethylene glycol 400, sorbitan monooleate polysorbate 80
Printing ink: opacode Black, n-Butyl alcohol, propylene glycol

The capsules are packed in polyvinyl chloride/aluminium blisters.

2.2.2. Active Substance

Tafamidis meglumine which has the chemical name d-Glucitol, 1-deoxy-1-(methylamino)-,2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate is a is the micronized meglumine salt of Tafamidis. It is a white to pink solid which is a slightly soluble molecule in water and pH dependant. The chemical structure of the active substance is:



Three solid state forms of tafamidis have been detected: two crystalline forms (Form M and Form I) and an amorphous form. The M and the I forms are the same polymorphic form based on XRPD and DSC analysis. The drug substance manufacturing process controls for the production of the M form. Tafamidis does not have chiral center.

Manufacture

Tafamidis meglumine is synthesised in a six-step process, starting from 1 key starting material.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

Specification

The active substance specification includes tests for appearance, identification (IR, NMR-1H, HPLC), water content, specific rotation, residue on ignition, heavy metals, lithium, assay (HPLC, 98.0-101.0%), polymorph, assay of meglumine (IC), particle size (Lasser diffraction), Escherichia coli (Ph Eur), purity (HPLC),and residual solvents (HS-GC).

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Batch analysis data of 5 batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies were carried out for non micronized (3 batches) and for micronized drug substance (3 batches) under ICH conditions (up to 6 months at 40°C / 75 % RH and up to 60 months at 25°C / 60 % RH). Parameters studied were: appearance, water content, assay by HPLC, purity by HPLC and

polymorphism for all conditions. Tests for agglomerization assay and E. coli control were added for the long term condition study and for the micronized drug substance only.

A photostability study for a batch of tafamidis was performed according with ICH guidelines.

The proposed retest period is justified based on the stability results.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The physicochemical and biopharmaceutical properties of the active substance that are relevant for product performance were identified and assessed. In order to better control the particle size of the drug substance a jet milling step was added into the production of the tafamidis drug substance for use in primary drug product stability studies and for commercial product.

During development it was shown that tafamidis active substance, when formulated in a hard gelatin capsule with standard excipients, formed a rigid gel structure upon contact with aqueous vehicles thereby affecting the dissolution rate from the solid dosage. Based on the initial dissolution results, it was decided to further enhance drug dispersibility and the dissolution rate using a soft gelatin capsule dosage form.

Based on this the strategy was to prepare a water-dispersible drug suspension that would not form a gel upon contacting water and encapsulate the suspension in a soft gelatin capsule. A suspension formulation was required as tafamidis showed poor solubility in many of the vehicles commonly used in formulating soft gelatin capsules and thus eliminated the option of developing the drug in a solution form.

The selection of excipients and their corresponding levels was based on in vitro dispersion, stability, and in vivo bioavailability studies. The selection and optimization of individual components of the proposed commercial formulation were discussed in detail. The chosen excipients in the capsule fill solution are: polyethylene glycol (suspending vehicle), sorbitant monoolate (surfactant/wetting agent), polysorbate 80 (surfactant/wetting agent). The excipients in the capsule shell are: gelatine, propylene glycol, purified water, 'Sorbitol special-glycerin blend' (d-sorbitol, 1,4 sorbitan, mannitol and glycerin) and titanium dioxide (E 171) and black printing ink.

All excipients used to manufacture of Vyndaquel meet compendial requirements except for Opatint White and Opacode Black ink.It is reported that Opatint White is a mixture of titanium dioxide (EP/USP) and glycerine (EP/USP). In-house specifications are described for Opatint White and Opacode Black.

A detailed description of the formulations used in the clinical studies is provided. The composition of the finished product used in the pivotal clinical trials is identical to that proposed for marketing.

The primary packaging product protective components are Aclar thermoformed individual product blister cavities containing one capsule. The cavity is heat sealed closed with an aluminum foil barrier lid stock. The primary blister packaging components are commonly used in pharmaceutical blister packaging. Stability studies showed that the selected blister components provide adequate product protection and are compatible with the dosage form.

Adventitious agents

The only excipient used in the manufacture of Vyndaqel that is from human or animal origin is gelatin. The gelatin is obtained from bovine bones that are free from skulls, spinal cord and vertebrae.

The gelatin used meets the criteria described in the monograph "Products with the risk of transmitting agents of animal spongiform encephalopathies" (no. 1483, Ph. Eur. 4th Ed. and any subsequently revised version). A TSE Certificate of Suitability for the gelatin has been provided.

Manufacture of the product

The preparation of the 20 mg tafamidis bulk capsules takes place in primarily in four steps. The first step is used to form the soft gelatin capsules. The second step is the preparation of the 20 mg tafamidis suspension. The third step is the encapsulation of the tafamidis suspension into the soft gelatin capsule and the fourth step is polishing and printing of the capsules.

The manufacturing process includes four major operations: production of the semi-solid gelatin mass material, preparation of the suspension, encapsualation and polishing and printing of the capsules,

Manufacturing process is well described and in-process controls are defined.

Considering the orphan drug status of tafamidis, full validation data are acceptable post approval. Nevertheless, detailed data obtained all along manufacturing of the three half scale batches already manufactured have been asked to confirm that the process is under control. All the data are not available yet so an enhancement of validation protocol is asked and results of validation batches are asked to be submitted post approval.

Product specification

The specification includes tests by validated methods for appearance, ,identity (HPLC, PDA), assay (HPLC, 95.0%-105%), impurities (HPLC), uniformity of dosage, dissolution, capsule fill water content, microbial limits (Ph Eur).

The test and limits of the release and shelf life specification for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.

3 pilot batches representative of the commercial drug product and 6 development batches for supportive stability studies data were provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

Stability of the product

Six months stability results are presented for 3 pilot batches packaged in ACLAR blister, stored under long-term (25 C/60% RH), intermediate (30°C/65 % RH) and accelerated (40 °C/ 75 % RH). These batches were tested for the following stability parameters: appearance, assay, purity, dissolution, capsule fill moisture, and capsule shell moisture. Microbial testing will be conducted every 12 months. The provided stability results are within specifications.

Photostability of the packaged product was proven. The thermal cycling study was successfully performed. 12 month stability data were provided for one pilot batch and showed no change in stability parameters.

Stress testing was performed to demonstrate the stability indicating nature of the analytical method used for the assay and impurities.

On the basis of the stability data available, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

- Validation data obtained on the 3 first commercial batches should be provided post approval.
- The identification for the primary packaging components should be added as a specification

2.3. Non-clinical aspects

2.3.1. Introduction

Tafamidis was developed as a specific stabiliser of TTR tetramer. It is intended for the oral treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy. This drug is an orphan medicinal product.

The nonclinical development of tafamidis was designed to comply with the (ICH) M3 [R1] guideline "Maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals" and relevant notes for guidance. Primary and secondary pharmacodynamics was performed in vitro, by non-GLP assays. Critical safety pharmacology and pharmacokinetic assays complied with GLP, although repeated dose pharmacokinetics was not performed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacologic activity of tafamidis was demonstrated only *in vitro*, through its binding to TTR at the thyroxine binding sites and stabilisation of the TTR tetramer under non-physiologic (acid and urea denaturation conditions) and physiologic conditions. The potency of tafamidis as a TTR stabiliser was reflected in the binding constants of tafamidisis derived from the monomeric subunit exchange time course experiments (KD1=2 nM and KD2=154 nM) and from isothermal titration calorimetry (KD1=3 nM and KD2=278 nM), conducted with purified TTR.

In order to further assess the ability of tafamidis to stabilise TTR, an in vitro study was performed using purified wild-type TTR and the two most prevalent amyloidogenic variants (V30M TTR and V122I TTR) at a physiologically relevant TTR protein concentration (3.6 µM) and using acidic denaturation conditions (pH 4.4-4.6). Tafamidis effectively inhibited fibril formation induced by acid denaturation in a concentration-dependent manner with similar potency for wild-type TTR, V30M TTR and V122I TTR,

reaching its EC50 at a tafamidis:TTR stoichiometry of <1 (EC50 was in the range of 2.7-3.2 μM, corresponding to a tafamidis: TTR stoichiometry range of 0.75-0.9).

Tafamidis is metabolized to an acylglucuronide in the nonclinical species (mouse, rat and dog) and in humans. The propensity for the acylglucuronide metabolite to bind to the transthyretin thyroxine binding site was not established (see the Discussion).

The extent of tafamidis binding to plasma proteins was evaluated using animal and human plasma. Although tafamidis binds to both TTR and albumin, the affinity of tafamidis for TTR (KD1=2 nM and KD2=154 nM) is substantially greater than that for albumin (KD = 2,500 nM). Hence, despite the significantly higher concentration of albumin (600 μM) relative to TTR (3.6 μM) in plasma, tafamidis was observed to bind specifically to TTR.

Primary pharmacodynamic studies *in vivo* were not performed by the applicant (see the Discussion).

Secondary pharmacodynamic studies

The applicant provided in vitro binding/ inhibition data from a non-GLP study testing more than 50 receptors/enzymes/ion channels including the thyroxine receptor. Beyond binding to TTR, the only other notable binding activity of tafamidis was observed on the δ-2 opioid receptor [in vitro binding affinity (IC50) = 8.3 mM], while no significant affinity was demonstrated for the kappa and mu opioid receptors. In a non-GLP functional assay using the hamster vas deferens to assess the functional significance of the binding to δ-2 receptors, tafamidis displayed an agonistic activity. However, the modest δ-opioid agonistic activity of tafamidis (EC_{50} >10 mM) combined with its very high plasma protein binding (>99%) suggest that adverse effects mediated through an interaction with the δ-opioid receptor would not be expected at the mean human steady-state C_{max} of 7.4 mM (2.28 μg/ml).

Non-GLP assays for cyclooxygenase (COX-1 and COX-2) inhibition by tafamidis were performed on recombinant enzymes and in human whole blood, demonstrating absence of inhibitory effects.

Although tafamidis binds to TTR at the thyroxine binding sites, the applicant maintained that treatment with tafamidis is not anticipated to result in an impact on thyroid function. The main plasma carriers of thyroxine are thyroid binding globulin (carrying 75% of the total circulating T4) and albumin, TTR being a tertiary carrier protein of plasma thyroxine, with only 1% of TTR tetramers transporting T4. In the pivotal clinical study Fx-005, there was no change in free or total plasma thyroxine levels and no effects on retinol-binding protein, thus showing the absence of effect of tafamidis on plasma thyroxine and retinol levels.

Safety pharmacology programme

The safety pharmacology of tafamidis was evaluated in the core battery of tests as specified in ICH S7A and S7B guidelines.

In a single-dose study (GLP) in rats assessing central nervous system changes, the oral administration of tafamidis at dose levels of 10, 30 or 100 mg/kg resulted in no behavioural changes when compared to the vehicle-treated group. However, a significant body weight loss was observed at the high dose in both males (2%) and females (3.1%).

In an *in vivo* cardiovascular and respiratory study (GLP) in telemetered Beagle dogs, following single oral doses of up to 300 mg/kg there were no dose-dependent or biologically significant tafamidis-related findings on heart rate, hemodynamic parameters, respiratory rate, arterial blood gases and core body temperature during the 24-hour post-dose monitoring period. A prolongation of QRS interval

(3% and 6% at 100 and 300 mg/kg, respectively) and a shortening of QTc interval (3 to 5% at 100 mg/kg and 4 to 6% at 300 mg/kg) was observed. In *in vitro* assays, a dose-dependent stimulation of IKr current attaining 10% at 300 mg/kg was detected.

In the same study, the mean maximum plasma concentration of tafamidis achieved in dogs following the 300 mg/kg dose was 141 µg/ml at 5 hours post-dose, corresponding to a concentration up to 62 times the mean human clinical steady-state C_{max} (2.28 µg/ml). Clinical observations of emesis (n=4) (see table 1), salivation (n=1) and leg twitching (n=1) were observed post-dose in the dogs at 100 and 300 mg/kg.

Table 1. Study SYI00009

Study Type	Study Number (location)	Species/ Strain	Dose (mg/kg)/ Route	Design	Clinical Observations	Cmax (µg/mL) Emesis NOEL	Mean Exposure (µg/mL) at 30 minutes postdose
Safety Pharmacology/ Cardiovascular	SYI00009 (Module 2.6.3, Table 2.6.3.4)	Dog/ Beagle	0, 10, 100, 300/ Oral gavage	4 females, escalating dose	**100 mg/kg:** Emesis in 2/4 animals **300 mg/kg:** Emesis in 4/4 animals	34.0	**10 mg/kg:** 31.2 **100 mg/kg:** 92.5 **300 mg/kg:** 99.2

Cmax = Maximum (peak) observed drug concentration; NOEL = No observed effect level.

Pharmacodynamic drug interactions

The applicant did not conduct specific pharmacodynamic drug interaction studies.

In a screening with small molecules, NSAIDs (diflunisal and diclofenac) were observed to exhibit TTR stabilisation through binding to the TTR thyroxine binding sites. As no PD interaction studies with NSAIDs were performed, the applicant presented the binding constants for tafamidis, diflunisal and diclofenac measured by isothermal titration calorimetry (ITC), see table 2.

Table 2

Drug	**Transthyretin (TTR)**		**Albumin**
	Kd1 (nM)	Kd2 (nM)	Kd (nM)
Diclofenac*	60	1,200	N/A
Diflunisal*	75	1,100	N/A
Tafamidis	3	278	2,500

2.3.3. Pharmacokinetics

The *in vivo* absorption, distribution, metabolism and excretion of tafamidis following single and/or repeated oral and intravenous administration was evaluated in 23 non-GLP and 10 GLP pharmacokinetic/toxicokinetic studies performed in mice, rats, rabbits and dogs. A non-GLP study to examine placental transfer and excretion in milk was performed in rats as part of the reproductive toxicity programme.

* Miller, SR, Sekijima Y and Kelly JW. Native state stabilization by NSAIDs inhibits transthyretin amyloidogenesis from the most common familial disease variants. *Lab Invest.* 2004 May;84(5):545-52.

Most of the pharmacokinetic parameters presented for inter-species comparison were obtained from acute administration. Data presented from repeated dose studies were obtained from the toxicokinetic data (see Discussion).

Method of analysis

The biological samples in the pharmacokinetic and toxicokinetic studies were analyzed by validated LC/MS/MS methodologies. 14C-tafamidis was used in the ADME study and in the placental and milk transfer study. Radioactivity was measured by liquid scintillation spectroscopy according to the laboratory's Standard Operating Procedures. The assessment of radioactive stability prior to and immediately after treatments showed that 14C-tafamidis was stable under the conditions used.

Absorption

In *in vitro studies,* tafamidis crossed readily Caco-2 monolayers in a passive transcellular pattern. Tafamidis was not a substrate of OAT (organic anion transporter), OCT (organic cation transporter), MRP2 (multidrug resistance-associated protein 2) or P-gp (P-glycoprotein) transporters, but showed an inhibitory effect on the OATP (organic anion transporting polypeptide), BCRP (breast cancer resistance protein) and MRP (multidrug resistance-associated proteins) transporters. Slight inhibition was observed on P-gp transporter at higher concentrations.

Bioavailability studies conducted over a 24-hour period in rats at doses 2 mg/kg and in dogs at doses 1 mg/kg demonstrated absolute bioavailability of 100% and 91%, respectively (based on AUC_{0-24}).

Drug exposure as measured by C_{max} and AUC_{0-inf} was dose-proportional up to a single dose of 30 mg/kg and showed an asymptotic trend to saturation with higher doses.

Pharmacokinetic parameters of tafamidis after a single oral administration (from preclinical studies conducted over a 168-hour period) are summarised in table 3 below:

Table 3

Species	Dose (mg/kg)[a]	Detection method	$T_{1/2}$ (hours)	T_{max} (hours)	C_{max} (µg/ml)	AUC_{0-inf} (µg*hr/ml)	V_Z/F[b] (ml/kg)
Rat[c]	3	^{14}C	43.1	2	11.3	368	265
Rat	3	LC-MS/MS	41.9	1	9.06	216	331
	10		28.5	0.5	35.3	512	283
	30		29.0	4	102	2590	294
Dog	30	LC-MS/MS	62.3	2	87.6	1455	342
	60		54.7	1.5	130	2260	461
	80		56.5	1.5	160	3390	500

[a] *Dose levels are expressed as Fx-1006 active ingredient. Human dose levels are based on a 60 kg body weight.*

[b] *V_Z/F have been calculated from the data presented in this table as dose (mg/kg)*1000/Cmax (µg/ml)*

[c] *Only values from male animals in plasma are reported for this study to allow comparison with other nonclinical studies which were conducted in male animals*

Tafamidis half life in plasma was approximately 29-43 hours in rats and 55-62 hours in dogs.

Following repeated doses, saturation of absorption in dogs and accumulation in all species tested, i.e. mice, rats, rabbits and dogs, was observed.

In rats, decreased exposure to tafamidis was observed with food intake.

There were no marked gender differences in pharmacokinetic parameters in mice, rats and dogs.

Distribution

Upon single oral administration in rats, tafamidis was subject to a widespread distribution and accumulated preferentially in the liver and in harderian glands. Except for these two organs, the organ/plasma ratio was always <1, indicating a selective distribution in the plasma compartment. The Cmax values for the majority of tissues occurred at 2 hours post-dose. Presence of tafamidis was still detected in most tissues at 168 hours post-dosing.

Tafamidis was observed to cross the placental barrier and distribute to the foetal tissues to an extent of 3-4% of the administered dose in rats. More than 30% of the dose of tafamidis was transferred to milk when administered to lactating rats. This matter is adequately reflected in section 4.6 of the SmPC.

Upon entering the blood stream, tafamidis was highly bound (> 97%) to plasma proteins and did not enter blood cells. In vitro, a mean percentage of plasma protein-bound tafamidis was 97.1, 99.0, 99.1 and ≥ 99.2% in mouse, rat, dog and human plasma, respectively.

Distribution volumes, as measured following intravenous administration of tafamidis, were small (316 ml/kg in rats and 317 ml/kg in dogs) and corresponded to the extracellular water content for both species.

In studies with oral administration of tafamidis, the apparent distribution volume of tafamidis was constant (around 300 ml/kg) irrespective of the species, at doses of up to 30 mg/kg. Above 30 mg/kg, it increased linearly with dose, presumably due to saturation of absorption.

Metabolism

In *in vitro* metabolism studies using subcellular fractions of liver from the non-clinical species (mouse, rat, rabbit and dog) and humans, relative metabolic stability of tafamidis was observed, with ≥ 94% of the parent molecule unchanged across all species. The small percentage of metabolic transformation was identified as a monoglucuronide (acylglucuronide) metabolite in mouse, rat, dog and human microsomal incubation mixture and as a monoxide metabolite in mice. No apparent qualitative gender differences were seen in the metabolite profiles.

In vivo, major metabolic pathways of tafamidis were described by plasma metabolite identification in mouse, rat, rabbit and dog. Three metabolic pathways were proposed: glucuronidation mediated by UGT, mainly 1A9, 1A1 and 1A3 and in a minor extent 1A6, 1A7, 1A8 and 2B7, sulphation and oxidation. Table 4 below summarises in vitro and in vivo metabolites identified in the species tested.

Table 4: *In vitro* hepatic and *in vivo* plasma metabolites of tafamidis

Species and strain	***In vitro* Metabolites* (Study N° 400447)**	**Metabolite* Relative Quantity (%) (Study N° 400447)**	***In vivo* Plasma Metabolites**	**Metabolite Plasma Relative Quantity (%)**	**Study number (*In vivo* corresponding study number)**
Mice CByB6F1 hybrid	acylglucuronide monooxide	9%	acylglucuronide monooxide	4.1 – 12.2 0.5 – 1.2	400554 (SYI00064)
Rats Sprague-Dawley	acylglucuronide	1%	acylglucuronide	3.5 – 16.1 0.3 – 11.9	400979 (SYI00012) 420372
Rabbits New Zealand	none detected	0%	monooxide	1.7 – 9.2	400605 (SYI00040)

Species and strain	*In vitro* Metabolites* (Study N° 400447)	Metabolite* Relative Quantity (%) (Study N° 400447)	*In vivo* Plasma Metabolites	Metabolite Plasma Relative Quantity (%)	Study number (*In vivo* corresponding study number)
white					
Dogs Beagle	acylglucuronide	2%	acylglucuronide sulfate conjugate	0.99 – 6.31 0.05 – 0.98	400980 (SYI00013)
Humans	acylglucuronide	1%	acylglucuronide	1.2 – 12.8	400553 and 400699 (Fx-002)

*Hepatic microsome

Tafamidis did not significantly inhibit CYP2C9/19, 1A2, 2D6 and 3A4/5. It showed a moderate inhibitory effect on CYP2C8.

Tafamidis induced CYP3A4 in cryopreserved human hepatocyte cultures from female but not from male donors. This effect was minimal in the presence of albumin. (See also PK drug-drug interactions).

Excretion

Following a single oral dose of 3 mg/kg 14C-tafamidis to rats, excretion was quite slow in both sexes with less than 67% of the administered radioactivity excreted by 48 hours post-dose. Excretion rates and routes were similar for both male and female rats, although excretion via urine appeared to be greater in males than in females. Excretion recoveries were greater than 87% in both sexes by 168 hours post-dose.

Tafamidis was readily excreted in the bile as the unchanged parent and the acylglucuronide metabolite, with nearly 50% of the radioactivity excreted via the bile in both male and female rats during the first 72 hours following administration. Additionally, enterohepatic recycling of approximately 42-77 % of biliary excreted radioactivity was observed.

Elimination of radioactivity occurred by both the urine and faeces, the majority of the administered radiolabelled compound (67-79%) being recovered in the faeces over the period 0 to 168 h post-dose, and 7-19% recovered in the urine over the same time period.

Metabolite analysis of faeces and urine samples showed that tafamidis was eliminated unchanged in faeces, whereas the major urinary metabolite was acylglucuronide.

PK drug-drug interactions

Tafamidis exhibited moderate inhibitor effects on CYP2C8.

Induction of CYP3A4 was observed in female (n=2), but not male (n=1) human hepatocyte cultures. More than 90% tafamidis was bound to TTR or albumin in plasma. Exposure of hepatocytes to tafamidis was much lower in presence of albumin and its effects on CYP3A4 were reduced. In a study where hepatocytes from one donor were exposed to tafamidis in the presence of the physiological concentration of 40 mg/ml albumin, tafamidis exhibited minimal impact on CYP3A4 activity.

Tafamidis did not interfere with the binding of cyclosporine, tacrolimus and warfarin (>90% initial binding to plasma proteins) and decreased the binding of prednisone by ~10% (79% initial binding to plasma protein). The clinical relevance of this displacement is unknown as the pharmacologic activity of prednisone requires metabolism to prednisolone, the active metabolite.

The effect of other drugs on the binding of tafamidis to TTR has not been evaluated.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity was assessed in Beagle dogs (see Table 5). No mortality or serious adverse effects were observed with single oral doses up to 600 mg/kg.

Table 5

Species/ Sex	Dose/Route	Approx. lethal dose/ observed max non-lethal dose	Major findings
Beagle dog/M+F	0 (M), 30 (M), 100 (M), 300 (M), 600 (M+F) mg/kg; oral gavage	600 mg/kg	1 M at 600mg/kg: ↑ ALP. *This was not observed in repeated dose studies and was not associated to increase in ALT or AST.*

Repeat dose toxicity

In repeat dose toxicity studies tafamidis administered orally was tested in mice up to 28 days, in rats up to 26 weeks and in Beagle dogs up to 39 weeks. At high doses, tafamidis caused mortality in mice (at doses ≥240 mg/kg), in rats (at doses ≥100 mg/kg) and in dogs (at doses ≥ 100 mg/kg). The NOAEL were 10 mg/kg in mice, 3 mg/kg in rats, 5 mg/kg in female dogs and 15 mg/kg in male dogs.

Table 6 summarises the main repeat-dose toxicity studies and their findings.

Table 6

Species/ Number/ group	Dose* (mg/kg/day) Route	Duration	NOAEL (mg/kg/day)	Major findings
Mice/CByB6F1 hybrid 10/sex/group (TK: 20/sex/group)	0, 10, 30, 45, 60, 120, 240[a], 480[b] Oral	28 days	10	**≥ 30 mg/kg**: Centrilobular single cell necrosis **≥ 120 mg/kg**: Centrilobular hypertrophy ↑ AST and ALT (only at this dose in males) ↓ corpora lutea **≥ 240 mg/kg**: Mortality (9M/10 and 5F/10 at 480 mg/kg and 6M/10 and 1F/10 at 240 mg/kg). ↓ motor activity, impaired gait, seizures, laboured respiration and hunched appearance, ↑ AST and ALT (only at this dose in females) White powder contents in the stomach Vaginal hyperkeratosis Estrous disruption Lymphoid depletion

Rats/SD 10/sex/group (TK: 6/sex/group Recovery: 5/sex/group for control and HD groups)	0, 10, 30, 100, 300[c] Oral	28 days + 14 days of recovery	10	≥ 30 mg/kg: ↑ liver relative weight, ↑ liver absolute weight (in females) ↑ creatinine (in males) ≥ 100 mg/kg: Mortality (3F at 100 mg/kg and 7M and 2F at 300 mg/kg) Scant faeces, hunched posture lethargy, rough hair coat, urine stained perineum, ↓ body weight, ↓ food consumption (in females), ↑ ALT, Cholesterol (in males) ↑ creatinine, ↑ glucose (in females) ↓ heart weights (in males) ↓ epididymis absolute weight ↑ uterus weights ↑ ovaries and thyroid absolute weight (in females) Thymic depletion (in females) Gastric impaction due to test material accumulation. 300 mg/kg: ↓ RBC, Hb, HCT, (in males only, no recovery) ↑ ALT and AST (in females) ↑ bilirubin and TG Stomach necrosis and distension with accumulation of test article Thymic depletion (in males) Tubular proteinosis and accumulation of red pigment in the tubules (in females)
Rat/SD 10/sex/group for the 13-w phase 10/sex/group for the 26-w phase (TK: 6/sex/group Recovery: 6/sex/group for control and HD groups)	0, 3, 10, 30 Oral	13 weeks + 4 weeks of recovery OR 26 weeks	3	**≥ 10 mg/kg**: ↑ BUN (in males) ↑ bilirubin (in females) ↑ liver relative weight (in males) **30 mg/kg**: ↓ Hb and ↑ PT (in females) ↑ fibrinogen and ↑ creatinine (in males) ↑ liver absolute weight (in males) Enlarged or discoloured lymph nodes Thymus atrophy Renal pelvis dilation Enlarged pituitary gland
Dog/Beagle 3/sex/group (Recovery: 2/sex/group for control and HD group)	0, 10, 100, 300→200[d] Oral	28 days + 14 days of recovery	10	**≥ 100 mg/kg**: Mortality (3 at HD and 2 at MD). Vomiting and abnormal feces. Enhanced salivation, lethargy, thinness, ataxia, head bobs, twitching, coldness to touch. ↑ Ca (in females) Discoloration of spleen and thymus. Enlarged cervical lymph node. **300→200 mg/kg:** ↓ food consumption ↓ monocytes and ↑ MCHC (in males). ↑ PAL, GGT, bilirubin, BUN (in males) ↓ cholesterol (in females) Reddish discoloration of the gastric and intestinal mucosa (in 1F)

Dog/Beagle 3/sex/group for the 13-w phase 3/sex/group for the 39-w phase (TK: 6/sex/group Recovery: 2/sex/group for control and HD groups)	0, 5, 15, 45 Oral	13 weeks + 4 weeks of recovery OR 39 weeks	5 (F) 15 (M)	**≥ 15 mg/kg**: ↑ RBC, Hb in females) ↓ ovaries absolute weight **45 mg/kg**: ↑ incidence of soft, mucoid, discolored feces and feces with apparent blood. ↑ Monocytes and ↓ eosinophils (in females) ↑ Pituitary absolute weights ↑ increase in emesis (in female)

* Expressed as Fx-1006 equivalents
[a] Treatment discontinued at D3
[b] Treatment discontinued at D8
[c] Treatment discontinued at D10
d The high dose was reduced from 300 mg/kg to 200 mg/kg on Day 8 for females and Day 9 for males

Genotoxicity

Tafamidis was tested in the *in vitro* bacterial reverse activation mutation assay (Ames test), the *in vitro* human lymphocyte chromosomal aberration assay and the *in vivo* oral rat micronucleus assay. The Ames test and the micronucleus test were negative. In the chromosomal aberration assay, a dose-dependant increase of polyploidy was observed at 100 and 200 µg/ml in the presence of S9.

Carcinogenicity

A 26-week carcinogenicity study in transgenic rasH2 mice was conducted by the oral (gavage) route of administration – see table 7 below.

Table 7:

Species/ Number/ group	**Dose (mg/kg/day) Route**	**Duration**	**NOAEL (mg/kg/day)**	**Major findings**
Mouse/Tg.rasH2 25/sex/group (TK: Mouse/CGyB6F1 10 or 40/sex/grp)	Fx-1006A 0 (vehicle), 0 (water), 10, 30, 90 Oral	26 weeks	NOAEL (general toxicity) = 10 (M) 30 (F) NOAEL (carcinogenicity) ≥ 90	No treatment-related neoplastic lesions. Higher incidence of spleen and lung tumors with the positive control urethane. ≥ 30 mg/kg: ↓ body weight (in males) ↑ liver weight and ↓ kidney weight (in males) Nephrosis (in males) Centrilobular hypertrophy and single cell necrosis (in males) 90 mg/kg: Centrilobular hypertrophy and single cell necrosis (in males)

No long-term studies were conducted by the applicant. Tafamidis did not show carcinogenic potential in the model which is recognised as responsive to both genotoxic and non-genotoxic carcinogens. The carcinogenic potential of tafamidis was not studied in a long term rodent carcinogenicity study. This was considered acceptable given the severity and low incidence of the disease together with the fact that no alert signals were identified in the nonclinical studies conducted including the TgrasH2 mouse model.

Reproduction Toxicity

The reproductive toxicity of tafamidis was studied in line with the requirements of the S5 ICH guideline.

The main reproductive and developmental studies and their findings are summarised in table 8.

Table 8

Study type/ Study reference / GLP	Species; Number/ sex/group	Dose (mg/ kg/day) Route	NOAEL (mg/kg/day)	Major findings
FERTILITY AND EARLY EMBRYONIC DEVELOPMENT				
Fertility and general reproduction toxicity (SYI00060) GLP	Rat/SD 25/sex/group	Fx-1006A 0, 5, 15, 30 Oral	NOAEL (parental toxicity) ≥ 30 (M) =15 (F) NOAEL (reproduction) ≥ 30	Males: No treatment-related findings Females: 30 mg/kg: ↓ body weight and body weight gain, ↓ food consumption
EMBRYO-FETAL DEVELOPMENT				
Developmental Toxicity Study in Rats SYI00039 GLP	Rat/SD 25F/group (TK: 6F/group)	Fx-1006A 0, 15, 30, 45 Oral	NOAEL (maternal toxicity) = 30 NOAEL (reproduction) ≥ 45 NOAEL (development) = 15	≥ 30 mg/kg: ↓ maternal body weight gain (during the first 3 days of treatment at MD). ↓ fetal weight 45 mg/kg: maternal mortality (4 dams) associated with dehydration, hypothermia, hunched posture, sparse hair, abnormal feces. ↓ maternal body weight and body weight gain No effects on reproduction parameters. No teratogenic effects
Developmental Toxicity Study in Rabbits SYI00040 GLP	Rabbit/NZW 20 F/group (TK: 3F/group)	Fx-1006A 0, 0.5, 2, 8 Oral	NOAEL (maternal toxicity) = 0.5 NOAEL (reproduction) = 2 NOAEL (development) = 0.5	≥ 2 mg/kg: ↓ maternal body weight gain ↑ number of supernumerary thoracic ribs and thoracic vertebrae ↓ number of lumbar vertebrae 8 mg/kg: Abortion in 2F, Abnormal feces ↓ body weight and food consumption Increased late resorptions, ↓ fetal body weight, ↑ number of fetuses and litters with any alteration observed, In 3 fetuses from 2 litters: depressed eye bulges, small eyes and small eye sockets. ↓ number of ossified fore- and hind-limb phalanges

PRE- AND POSTNATAL DEVELOPMENT				
Developmental and peri/postnatal reproduction toxicity study SYI00068 GLP	Rat/SD 25F/group	Fx-1006A 0, 5, 15, 30 Oral	NOAEL (F0) = 5	**F0 dams:** ≥ 15 mg/kg: Mortality (4F/25 at MD and 20F/25 at HD were sacrified due to no surviving pups). ↓ body weight gain, ↓ food consumption 30 mg/kg: Sparse hair coat
			NOAEL (F1) = 5	**F1 generation:** ≥ 15 mg/kg: ↓ number of pups, ↓ pup body weight ↓ viability index and live litter size. ↑ number of litter with no milk band, not nursing and with purple or black discoloration ↑ number of pups with no milk present in stomach. 15 mg/kg: ↑ number of pups with domed head, microphtalmia, lacrimation, peri-orbital alopecia, chromodacryorrhea ↓ body weight in the post-weaning period and food consumption Mortality (2M: 1 dead at PND38 and 1 sacrificed at PND111) Retardation in preputial separation ↑ number of animals who failed to learn during session of the watermaze No effect on mating or reproductive performance. No histopathological alteration of the brain. 30 mg/kg: All pups died between PND 1 to 4 ↑ number of pups with stomach and intestines filled with gas
			NOAEL (F2) = 5	**F2 fetuses** 15 mg/kg: ↓ fetal body weight (F) Rotated limbs

ns: not statistically significant

Toxicokinetic data

Exposure margins based on AUC and Cmax from repeated dose, carcinogenicity and reproductive toxicity are summarised in table 9.

Table 9

Type of study	Species	Duration	NOAEL (mg/kg/day)	AUC tafamidis (µg.h/ml) at NOAEL[a]	Cmax tafamidis (µg/ml) at NOAELa	Exposure margin[b] based on	
						AUC	Cmax
Repeated dose	Mouse	28 days	10	137.5	14.6	**3**	**6**
	Rat	26 weeks	3	368.5	24.6	**7**	**11**
	Dog	39 weeks	15 (M)	567	51.5	**11**	**23**
			5 (F)	444	30.2	**9**	**13**
Carcinogenicity	Mouse	26 weeks	90	1599.5	96.9	**32**	**43**
Reproductive toxicity	Rat	Segment II	15	1090	72.8	**22**	**32**
	Rabbit	Segment II	0.5	157	8.14	**3**	**4**

a: AUC and Cmax on the last time point. Gender and time point of determination are only specified if the difference was considered relevant. Otherwise, average values are given.
b Animal/human exposure ratios calculated from tafamidis human steady state values of Cmax=2.28 µg/ml and AUC24h= 49.75 µg.h/ml obtained in typical subject of 70 kg, less than 60 years old, with normal hepatic function and with unknown food intake following 20 mg daily dosing (Study Fx-PopPK-001)

Local Tolerance

No local tolerance studies were performed.

Other toxicity studies

Tafamidis was not phototoxic in a study in pigmented rats. No specific immunotoxicity studies were submitted. With respect to impurities, one synthetic intermediate (DCBC) gave a positive genotoxic response in silico. DCBC is highly reactive and unstable in aqueous media and thus, no Ames test could be conducted.

2.3.5. Ecotoxicity/environmental risk assessment

At the time of the tafamidis application for orphan medicinal product designation, the applicant estimated the prevalence of Familial Amyloid Polyneuropathy (FAP) in the European Union as 0.1 in 10,000 persons. The predicted environmental concentration (PEC) in surface water was calculated as follows.

$$PEC_{surfacewater}\ [mg/l] = \frac{DOSEai * Fpen}{WASTEWinhab * Dilution}$$

DOSEai Maximum daily dose of active ingredient consumed per inhabitant [20 mg/day]

Fpenrefined Fraction of market penetration [0.00001]

WASTEWinhab Amount of Wastewater per inhabitant per day [200 L/inh/d]

Dilution Dilution factor [10]

PECsurfacewater Local surface water concentration [µg/L]

$$PEC_{surfacewater}\ [mg/l] = \frac{20\ mg/inh/d * 0.00001}{200\ l/inh/d * 10} = 1.0 \times 10^{-7}\ mg/l$$

The resulting PECsurfacewater of 0.0001 µg/l was below the action limit of 0.01 µg/l. (See discussion).

Table 10 Summary of main study results

Substance (INN/Invented Name):Tafamidis meglumine			
CAS-number (if available): 951395-08-7			
Phase I			
Calculation	Value	Unit	Conclusion
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.0001	μg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No

2.3.6. Discussion on non-clinical aspects

Pharmacology

Tafamidis is a stabilizer of the transthyretin (TTR) tetramer. By binding to TTR tetramer, tafamidis inhibits tetramer dissociation and can disrupt progression of ATTR by preventing dissociation into monomers. The extent of tafamidis binding to plasma proteins was evaluated using animal and human plasma. Compared to other plasma proteins, tafamidis was observed to bind to TTR with high affinity.

Tafamidis is metabolized to an acylglucuronide in the nonclinical species (mouse, rat and dog) and in humans. The CHMP considered that the propensity for the acylglucuronide metabolite to bind to the TTR thyroxine binding site was not established, but was of the view that this metabolite would not be likely to contribute to the pharmacological activity of tafamidis, as it was not detected in human plasma following a single 20 mg/kg dose of ^{14}C-labeled tafamidis meglumine.

No *in vivo* studies were performed by the applicant. The CHMP considered that at the time of the preclinical development of tafamidis, an animal model of ATTR-PN that would reflect the clinical disease or resemble the pathology was not available, and that none of the transgenic animals described in the literature reproduce the pathology seen in ATTR patients. The CHMP agreed to the justification for absence of these studies.

With respect to secondary pharmacodynamic effects, a dose-dependent agonistic effect at δ-2 opioid receptors was observed. Considering that δ-2 opioid agonists are known to activate the chemoreceptor trigger zone (CTZ) leading to the stimulation of the vomiting center (VC)• and following observation of emesis in dog induced in a concentration dependent manner, the CHMP discussed clinical relevance of this putative effect on the CNS, especially after repeated administration. In this context, the CHMP considered that tafamidis was not associated with increased incidence of nausea or vomiting in clinical studies and that, given the limited accumulation potential of tafamidis, plasma concentrations in humans were not likely to reach sufficient levels to cause emesis in the clinical setting. Thus, the CHMP concluded that this non-clinical finding was not of a clinical relevance.

The safety pharmacology of tafamidis was evaluated in the core battery of tests as specified in ICH S7A and S7B guidelines.

Tafamidis was tested for its effects on CNS in an acute neurotoxicity study in rats. It induced no adverse neurological effects up to 300 mg/kg, although body weight loss was observed at the high dose in a small percentage of both males (2%) and females (3%). The CHMP was of the view that this finding was of no clinical relevance.

• Blancquaert et al, 1986; Kohl and MacDonald, 1991

In vivo, no significant tafamidis-related findings on heart rate, hemodynamic parameters, respiratory rate, arterial blood gases and core body temperature were seen in beagle dogs. However, the canine cardiovascular safety pharmacology assessment of tafamidis identified a statistically significant shortening of the QTc interval and lengthening of the QRS interval at doses 100 and 300 mg/kg. The CHMP considered these ECG observations in the context of clinical relevance and was of the opinion that given the severity of the disease and the fact that no cardiovascular safety concerns arose from clinical assessment, these non-clinical findings would not impact negatively on the positive benefit-risk balance of the product.

Emesis, salivation and leg twitching were observed post-dose in the dogs at high doses (≥100 mg/kg). These findings were coherent with those observed at similar doses in the toxicology studies and their clinical relevance was considered limited by the CHMP, as these effects were observed at dose levels and maximum plasma concentrations significantly higher than those relevant to the clinical use of tafamidis.

The CHMP considered that no pharmacodynamic interaction studies were conducted, in particular those with non-steroid anti-inflammatory drugs (NSAIDs), as NSAIDs (diclofenac and diflunisal) were observed to bind to the TTR thyroxine binding sites. The applicant presented the respective binding constants (see Results – table 2), suggesting that tafamidis will preferentially bind to TTR, even in the presence of diflunisal or diclofenac and that no significant pharmacodynamic drug interaction would be expected. This was accepted by the CHMP.

Pharmacokinetics

The PK studies addressed pharmacokinetics of tafamidis adequately. Nevertheless, the CHMP noted that most of the pharmacokinetic parameters presented for inter-species comparison were obtained from single administration studies. Data presented from repeated dose studies were obtained from the toxicokinetic studies. During their review, the CHMP discussed the level of information these available data give about ADME at pharmacological doses and data necessary to establish the best dosing regimen. Since there is no relevant preclinical disease model, the CHMP considered that the best dose regimen was established from understanding of in vitro and ex vivo PK/PD experiments, combined with an extrapolation of clinically observed pharmacokinetics to select a dose that would achieve therapeutically relevant concentrations. In this context, the CHMP accepted that multiple dose studies in nonclinical species at pharmacologically relevant doses were not used for that purpose. Furthermore, as clinical data were considered sufficient to endorse the therapeutic use of tafamidis, the CHMP concluded that no further non-clinical data need to be generated.

The methods of analysis applied to study the pharmacokinetics of tafamidis were adequate for the identification and quantification of the parent compound and metabolites in the performed assays.

Bioavailability of tafamidis was complete. Saturation of absorption in dogs and accumulation in mice, rats and dogs after repeated dosing was observed. Tafamidis was widely distributed, highly bound to albumin and crossed the placental barrier. The CHMP considered that as there are no adequate data on the use of tafamidis in pregnant women and the potential risk for humans is unknown, section 4.6 of the SmPC will specify that tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception.

The metabolism of tafamidis was not extensive. The major metabolite identified across all tested species (except for rabbits) was acylglucuronide; in humans, this was the only metabolite detected. The CHMP considered that acylglucuronides were increasingly identified as reactive electrophilic metabolites capable of undergoing intermolecular reactions with proteins, leading to covalent drug-protein adducts and initiating toxicity/immune responses, the liver being the target organ*.

* Bailey and Dickinson, 2003; Skonberg et al, 2008

Considering the observed hepatic accumulation of tafamidis with concomitant increase in liver weight and also alteration of liver enzymes in all tested species following administration of high doses of tafamidis, the CHMP was of the opinion that the pharmacovigilance strategy as described in the Risk Management Plan needs to be in place to monitor whether this potential toxic mechanism could be of clinical relevance. In particular, AE-specific questionnaires are to be utilised on receipt of a report suggestive of hepatotoxicity in order to obtain complete details of the event, allowing for a detailed review and establishing its relationship to the drug.

Excretion of tafamidis was slow with a half life of about 45 hours. Studies in rats showed that tafamidis is subject to enterohepatic re-cycling. Tafamidis was mainly excreted in faeces as intact substance, while metabolized material was excreted in urine as acylglucuronide conjugate, the only metabolite found in humans, detected in plasma at a proportion of 1-12%.

The CHMP considered that the inhibition of CYP2C8 and induction of CYP 3A4 by tafamidis is not likely to interfere with the metabolism of drugs being substrates of these enzymes, as tafamidis was highly bound to proteins in plasma and the free tafamidis concentration does not reach a sufficient level to produce either inhibition of CYP2C8 or induction of CYP 3A4. Furthermore, the CHMP took into consideration that in healthy volunteers, tafamidis did not induce CYP3A4.

Toxicology

The applicant submitted comprehensive results of non-clinical toxicology testing.

No mortality or serious adverse effects were observed with single oral doses of up to 600 mg/kg in Beagle dogs. This is approximately 1 900 fold of the intended clinical human dose (0.175 mg/kg or 12.2 mg/70 kg human tafamidis equivalent), demonstrating a large safety margin for acute toxicity of the drug. Thus, the CHMP considered that the acute oral toxicity of tafamidis is low, this being indicative of a low risk for overdose.

In repeat dose toxicity studies tafamidis administered orally was tested in mice up to 28 days, in rats up to 26 weeks and in Beagle dogs up to 39 weeks. The NOAEL in mice was 10 mg/kg, the safety margins were quite large ranging from 3 and 6 (from 28-day mouse repeat dose study) to 32 and 42 (from the mouse carcinogenicity study) based on AUC and Cmax ratio, respectively, i.e. indicating a good safety profile of tafamidis. Tafamidis was also considered to be well-tolerated in the rat at dose levels up to 10 mg/kg/day for 26 weeks, providing AUC exposure ratios of at least 24-fold based on the human AUC at steady state. In the dog, at dose levels up to 15 mg/kg in males and 5 mg/kg in females for 39 weeks, the exposure ratios of at least 11-fold in males and 9-fold in females based on the human AUC at steady state were achieved at the no-observable-effect level.

The CHMP noted that liver appeared as the target organ for toxicity in the different species tested. Increased liver weight, increased bilirubin and changes in liver enzymes were observed in rats and dogs. The CHMP considered that the hepatic findings were observed at safety margins >3 and were reversible. Furthermore, the CHMP was of the opinion that liver function can be easily monitored via standard biochemical parameters in clinical practice and concluded that monitoring the potential risk of hepatotoxicity in the post-authorisation setting, as described in the Risk management plan was appropriate.

Tafamidis was tested in the conventional battery of genotoxicity tests. The Ames test and the micronucleus test were negative. The CHMP noted that in the chromosomal aberration assay in human peripheral lymphocytes, a dose-dependant increase of polyploidy was observed in the presence of S9. Considering the unclear relevance of the finding and the large safety margins regarding micronucleus induction (>70) as well as the safety margin regarding polyploidy in the chromosome aberration assay (=18), the CHMP concluded that in the context of a serious disease with a lack of therapeutic options, this finding did not impact negatively on the benefit-risk balance of tafamidis.

No carcinogenic potential was observed in transgenic rasH2 mice treated with doses of up to 90 mg/kg for 26 weeks. The CHMP noted that no long-term studies were conducted, but given the therapeutic indication, particularly the severity of the disease, this was considered acceptable. Some deviations from GLP were observed in the conduct of the carcinogenicity study, but the CHMP was of the opinion that these would not hamper the scientific validity of the results.

The CHMP considered that the fertility study in rats did not reveal any concerns regarding reproductive toxicity in males or females. Because no reproductive effects occurred at the highest dosage tested, the paternal and maternal NOEL for reproductive toxicity of tafamidis is greater than 30 mg/kg/day, providing a human equivalent dose (HED) of 4.8 mg/kg; this is a dose level approximately 17 times the anticipated clinical human dose of 0.285 mg/kg.

In the rat developmental (embryo-foetal) study, tafamidis induced maternal toxicity (decreased body weight at 30 mg/kg, mortality at 45 mg/kg) and foetotoxicity (decreased body weight at 30 mg/kg), but was not teratogenic.

In a developmental (embryo-foetal) toxicity study in rabbits, a slight increase in skeletal malformations and variations, abortions in few females, and reduction in foetal weights were observed at an AUC ratio of 3.2-fold, based on the human AUC at steady state.

In the rat peri- and post-natal development study with tafamidis, decreased pup survival and reduced pup weights were noted following maternal treatment during pregnancy and lactation at doses of 15 and 30 mg/kg. Decreased foetal weights in males were associated with delayed sexual maturation (preputial separation) and impaired performance in a water-maze test for learning and memory. Furthermore, hyperactive-like behaviour was identified in the pups. The CHMP discussed the possibility that some mild disturbance of the maternal thyroid function during foetal development might have been the cause of the neuro-behavioural dysfunction in the pups. However, this possibility was not confirmed and the CHMP agreed that further investigation is not required. The NOAEL for viability and growth in the F1 generation offspring following maternal treatment during pregnancy and lactation with tafamidis was 5 mg/kg (HED=0.8 mg/kg), a dose approximately 2.8-times the anticipated clinical human dose.

Non-clinical data relevant to reproductive toxicity are summarised in section 5.3 of the SmPC and reproductive toxicity is listed among the important potential risks in the RMP. In the absence of relevant clinical data the CHMP was of the opinion that tafamidis should not be recommended during pregnancy and contraceptive measures need to be advised. This is reflected in section 4.6 of the SmPC as follows:

"Women of childbearing potential

Contraceptive measures should be used by women of childbearing potential during treatment with Vyndaqel, and for one month after stopping treatment, due to the prolonged half life.

Pregnancy

There are no data on the use of Vyndaqel in pregnant women. Studies in animals have shown reproductive toxicity. Vyndaqel is not recommended during pregnancy and in women of childbearing potential not using contraception."

Despite making this recommendation, the CHMP acknowledged that in clinical practice women treated with tafamidis may become pregnant and considered that a monitoring programme (Tafamidis Enhanced Surveillance for Pregnancy Outcomes, TESPO) will be in place in order to collect relevant clinical data, as described in the RMP.

Furthermore, the CHMP considered that thyroid function was not measured in pregnant animals and since tafamidis binds to one of the thyroxin binding proteins, a subtle effect could have occurred without a clear expression on the thyroid weight or histopathology in the pre-clinical testing. Therefore, even though relevant effect on the thyroid function was not identified in the pre-clinical or clinical setting, the CHMP was of the opinion that it cannot be excluded that tafamidis treatment may have subtle impact on the thyroid function due to the competition to the binding proteins. In this context, the CHMP was of the opinion, that changes of thyroid function should be listed as an important potential risk in the RMP.

No local tolerance studies were performed by the applicant. The CHMP considered that the effects on the gastrointestinal tract were evaluated during the repeated dose toxicity studies.

Other studies
One synthetic intermediate (DCBC) gave a positive genotoxic response *in silico*. DCBC is highly reactive and unstable in aqueous media and thus, no Ames test could be conducted. The CHMP considered that the manufacturing process is able to purge an excess of un-reacted DCBC if present from step 1, DCBC was not observed within the assay limits with a LOQ of 8 ppm. The CHMP concluded on a negligible risk for the treated population.

Environmental risk assessment

Tafamidis PEC surface water value is below the action limit of 0.01 µg/l. Therefore, the CHMP agreed that a phase II risk assessment was not needed.

Given the fact that tafamidis is an ionisable compound, the CHMP recommended that the applicant should conduct study OECD 107 to determine log Dow and perform assessment of the persistent bio-accumulative and toxic (PBT) potential of tafamidis accordingly.

2.3.7. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

With respect to the Environmental Risk Assessment, the Applicant should perform a log Dow determination according to the OECD 107 guideline and assess the persistent bio-accumulative and toxic (PBT) potential of tafamidis accordingly. It is noted that the results should be available by the end of IQ 2012.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 11				
Protocol	Phase	Status	Population	Endpoints
Fx-002	I	Completed	Healthy male and female volunteers (N=61; 43 tafamidis, 18 placebo)	Safety, tolerability, PK, PD (TTR stabilisation) of single and multiple tafamidis doses
Fx-003	I	Completed	Healthy male volunteers (N=19 tafamidis; 10 fasted, 9 fed)	Safety, tolerability, PK (tafamidis PK profile and effects of food on PK), PD (TTR stabilisation)
Fx-004	I	Completed	Healthy male volunteers (N=30 tafamidis; 10 (1 x 20 mg) soft gelatine capsule, 10 (2 x 10 mg) soft gelatine capsule, 10 oral solution)	Safety, tolerability, tafamidis PK profile, and bioequivalence of formulations, soft gelatine capsule and solution
Fx1A-105	I	Part 1 Completed Part 2 Ongoing	Part 1: Moderately hepatically impaired subjects (N=9) and healthy volunteers (N=9) enrolled Part 2: Mild hepatically impaired subjects (N=9) and healthy volunteers (N=9) targeted	Safety, tolerability, PK (tafamidis profile and effects of hepatic impairment on PK parameters)
Fx1A-107	I	Completed	Healthy volunteers (N=6)	Safety, tolerability, PK (tafamidis absorption and elimination profiles)
Fx1A-108	I	Completed	Healthy volunteers (N=14)	Safety, tolerability, PK (tafamidis profile and effects of food on PK parameters) with final formulation (soft gelatine capsule)
Fx1A-109	I	Completed	Healthy Volunteers (N=16)	CYP3A4 induction potential of tafamidis (midazolam); safety and tolerability of co-administration of tafamidis/midazolam
Fx1A-201	II; open label	Completed	Non-V30M ATTR-PN patients (N=21 representing eight different mutations)	Safety: Adverse events, physical examinations, laboratory testing, ECGs, 24-hour Holter monitoring, echocardiography, vital signs, concomitant medications Efficacy: TTR stabilization, NIS, Norfolk QOL-DN, NCS, Karnofsky Index, HRDB, mBMI, SF-36, NT-pro-BNP and troponin I. Pharmacokinetics. TTR sequencing.

Table 11				
Protocol	Phase	Status	Population	Endpoints
Fx1B-201	II; open label	Completed	V122I and wild-type ATTR-CM patients (N=35; 31 wild-type, four V122I)	Safety: Adverse events, laboratory testing, echocardiography, ECGs, 24 hr Holter monitoring, chest x-ray, physical examinations, vital signs, concomitant medications Efficacy: NYHA, Patient Global Assessment, TTR stabilisation, cardiac MRI, troponin I and T, NT-pro-BNP levels, 6-minute walk test, KCCQ, SF-36. TTR sequencing.
Fx-005	II/III; double-blind, randomized, placebo-controlled	Completed	V30M ATTR-PN patients (N=128; 65 tafamidis, 63 placebo)	Safety: Adverse events, laboratory testing, ECGs, echocardiography, vital signs, physical and eye examinations Co-primary: NIS-LL and Norfolk QOL-DN; Secondary: TTR stabilisation, NCS, QST, HRDB, mBMI, Σ7 NTs nds, Σ3 NTSF nds Pharmacokinetics
Fx-006	II/III; 1-year open-label extension to Fx-005	Completed	V30M ATTR-PN patients who complete Protocol Fx-005 (N=86, 45 previously on tafamidis, 41 previously on placebo, 85 received ≥1 dose)	Safety: Adverse events, laboratory findings, ECGs, Holter monitoring, vital signs, echocardiography, physical and eye examinations, concomitant medications Efficacy: NIS-LL, Norfolk QOL-DN, TTR stabilization, NCS, QST, HRDB, mBMI, skin biopsy for IENF, troponin I and NT-pro-BNP levels Pharmacokinetics
Fx1A-303	III; open-label	Ongoing	Patients who complete Protocol Fx-006 or Protocol Fx1A-201 (N=100 target)	Safety: incidence of AEs, physical examinations, use of concomitant medications, and vital signs Efficacy: NIS, Norfolk QOL-DN, Karnofsky
Fx1B-303	III; open label	Ongoing	V122I and wild-type ATTR-CM patients who complete protocol Fx1B-201 (N=31)	Safety: incidence of AEs, ECGs, echocardiography, laboratory testing, physical examinations, use of concomitant medications, and vital signs Efficacy: Patient Global Assessment, NYHA, KCCQ, 6-minute walk test, troponin I and T and NT-pro-BNP, mortality and hospitalisation

2.4.2. Pharmacokinetics

Absorption

In a phase I ADME study with a single 20 mg dose in healthy volunteers (Fx1A-107), tafamidis was rapidly absorbed with a T_{max} of 0.5 h and mean C_{max} of 1430.93 (SD 91.0) ng/ml. A mean C_{max} of 1574.6 ng/ml (SD108.8) was observed for ^{14}C-tafamidis equivalents.

The full plasma time profile for tafamidis and ^{14}C-tafamidis equivalents was well characterised. Mean $AUC_{0-\infty}$ derived from plasma concentration profile for tafamidis and ^{14}C-tafamidis equivalents was 47 864.31 (SD 11 380.38) ng.h/ml and 66 282.59 (SD 15289.28) ng.h/ml, respectively. The mean apparent total clearance for tafamidis and ^{14}C-tafamidis equivalents was 0.44 (SD 0.12) l/h and 0.32 (SD 0.07) l/h, respectively. Mean $T_{½}$ of the terminal elimination phase was 53.86 (SD 16.04) h and 64.23 (SD 16.37) h for tafamidis and ^{14}C-tafamidis equivalent, respectively.

Bioequivalence

During the development of tafamidis, three formulations were tested:

- The initial formulation, a hard gelatin capsule, was abandoned due to low bioavailability and is not described further.
- Tafamidis in 7.5% vitamin E TPGS solution (used in studies Fx-002 and Fx-003)
- Formulation of tafamidis meglumine soft gelatin capsules (used throughout the remaining clinical pharmacology studies and all clinical efficacy studies).

In Study Fx-004, bioequivalence was concluded for the 20 mg tafamidis meglumine in solution and as soft gelatine capsule based on the 90% CI for the ratio of the geometric means for AUC_{0-120} and Cmax.

Food effect

In study Fx-003 (a phase I, parallel-group study of an orally administered single dose of tafamidis meglumine in normal, healthy male volunteers under fed or fasted conditions), C_{max} was 32.3% lower and AUC_{0-120} was 11.1% lower in fed state.

In a phase I study evaluating the effects of food versus fasting state (Fx1A-108), following administration of the 20 mg tafamidis soft gelatine capsule, T_{max} occurred at a median of 1.75 h post-dose (range 0.50 to 6.00 h) under fasted conditions as compared to the median of 4 h post-dose (range 1.50 to 12.00 h) under fed conditions. AUC_{last} was equivalent in fed and fasted state and C_{max} was 23% lower in fed state.

Distribution

Distribution was estimated based on PK population analysis. Volume of distribution of the central compartment (Vc/F) and volume of distribution of the peripheral compartment (Vp/F) estimates were 0.482 L (95% CI: 0.366, 0.598, RSE: 12.3%) and 18.9 L (95% CI: 17.6, 20.2, RSE: 3.43%), respectively (for a subject less than 60-year old, 70 kg weight, with a normal hepatic function).

Clearance and volume of distribution of tafamidis in central and peripheral compartments were related to body weight linearly for volume of distribution and in the power of 0.75 for clearance.

Tafamidis was highly bound to plasma proteins (>99.5%) as determined in more than one study.

Elimination

In a phase I ADME study with a single 20 mg dose in healthy volunteers (Fx1A-107), tafamidis was eliminated slowly with $T_{1/2}$ of 53.9 h and Cl/F of 0.44 L/h. The major circulating entity identified in plasma was the parent compound. Almost complete recovery (80.9% of the dose) was observed; in faeces and in urine 58.5% and 22.4% of the dose, respectively, was recovered.

Estimates of apparent total clearance (Cl/F) were consistent across studies using the 20 mg dose, i.e. 7.3, 6.5 and 7.0 ml/min from studies Fx1A-107, 108 and 109, respectively, and also with data from the population PK analysis and the renal clearance from study Fx-002.

Glucuronidation is considered the major metabolic pathway of tafamidis. Screening of 10 cDNA-expressed recombinant human UDP-glucuronyltransferase (UGT) enzymes suggested that the major UGT isoforms responsible for the formation of the monoglucuronide metabolite are UGT 1A9, 1A1 and 1A3. Minor activity was observed with isoforms 1A6, 1A7, 1A8 and 2B7.

Metabolite profiling in human plasma and structural identification of metabolites was carried out by LC-MS/MS (Q-Trap) using a combination of full scan and product ion techniques. The metabolite patterns from several plasma samples collected from Study Fx-002 indicated that unchanged parent and its aromatic carboxylic monoglucuronide (acylglucuronide) were the most prominent components in all investigated samples.

Dose proportionality and time dependencies

Following single-dosing tafamidis was observed to show linear dose proportionality in Cmax and AUC with doses up to 30 mg; between 30 and 60 mg the exposure was less than proportional indicating saturation of absorption rate above 30 mg. The dose linearity was similar for single and repeated administration of tafamidis. No time dependency was detected, which is consistent with the finding that tafamidis has no induction effect.

Steady-state PK parameters were as expected from single and multiple dose PK in healthy subjects. Results of once-daily dosing with 20 mg for 14 days demonstrated that steady-state was achieved by day 14. Cmax(ss) and Cmin(ss) were 2.7 and 1.6 µg/ml, respectively.
Steady state exposure was similar between males and females. Following administration of 20 mg tafamidis solution to females, exposure was similar to that seen in males in a separate food effect study (Fx-003). The mean peak plasma concentration was 1.12 µg/ml compared to 1.23 µg/ml in males and mean AUC_{last} was 60.8 µg·h/ml compared to 51.9 µg·h/ml in males. The mean terminal half-life was also similar between genders.

Estimates of inter-individual variability from population PK analysis expressed as CV% are: 30.6, 25.9 and 13.2 for CL/F, Vp/F and KA, respectively.

Intra-individual variability (ANOVA residual error) was estimated from bioequivalence and food effect studies. The intra-individual variability was estimated to be 14.5 and 12.3% for $AUC_{0\text{-last}}$ and C_{max}, respectively.

Special populations

- **Impaired renal function**

No specific PK study in renally impaired patients was performed. The effects of creatinine clearance on tafamidis PK were evaluated in the population PK analysis; pharmacokinetic estimates indicated no difference in steady-state clearance of tafamidis in patients with creatinine clearance <80 ml/min compared to those with creatinine clearance>80 ml/min.

- **Impaired hepatic function**

Study Fx1A-105 (Pharmacokinetics of Orally Administered Tafamidis (Fx-1006A) in Subjects with Hepatic Dysfunction) was conducted to describe and compare the pharmacokinetics (PK) of tafamidis in subjects with moderate hepatic dysfunction and gender-, age- and weight-matched normal healthy subjects. Subjects with moderate hepatic impairment showed a lower exposure than healthy subjects; in particular, decreased systemic exposure (approximately 40%) and increased total clearance (0.52 l/h vs 0.31 l/h) of tafamidis was observed in patients with moderate hepatic impairment (Child-Plough Score of 7-9 inclusive) compared to healthy subjects. These findings are attributed to a higher unbound fraction of tafamidis in patients with hepatic impairment.

- **Gender**

Similar PK profile was observed in males and females. The ratio of the geometric LS Means for $AUC_{0-\tau}$(ss) and Cmaxss for females to males was 100.53 and 98.48, respectively, with the corresponding 90% confidence intervals (CI) being 83.54 – 120.98 and 82.14 – 118.08.

- **Race**

Results from a population PK analysis on a pool of all Phase I and Phase II/III studies showed that race as a covariate was not found to be significant.

- **Weight**

Results from a population PK analysis on a pool of all Phase I and Phase II/III studies showed that clearance of tafamidis increased allometrically (coefficient of 0.75) with increasing weight.

- **Children**

There is no relevant use of Vyndaqel in the paediatric population.

- **Elderly**

Results from a population PK analysis on a pool of all Phase I and Phase II/III studies showed that at steady state following repeated of 20 mg doses once a day, apparent clearance for tafamidis for subjects >60 years was estimated to be 19% lower compared to those <60 years. Based on PK simulations the predicted maximum concentrations at steady state (Cmax,ss) estimated for elderly and non-elderly subjects were 2.76 and 2.28 µg/ml, respectively, indicating a 21% higher Cmax (ss) for elderly compared to non-elderly subjects.

- **Pregnancy**

There is no clinical experience in pregnant women. No information is available on the presence of tafamidis in human breast milk.

Pharmacokinetic interaction studies

- **In vitro**

CYP inhibition and induction studies with tafamidis have been performed using validated probe substrates. In vitro, tafamidis did not significantly inhibit CYP1A2, CYP2B6, CYP3A4, CYP2C9, CYP2C19, and CYP2D6; a moderate inhibition of CYP2C8 was observed. In addition, an equivocal effect of the CYP 3A4 induction potential of tafamidis in hepatocytes obtained from female subjects was demonstrated, which prompted an in vivo study.

- **In vivo**

In study Fx1A-109 utilising a CYP3A4 probe substrate (7.5 mg midazolam) to evaluate Cytochrome P450 3A4 Induction Potential, tafamidis did not induce CYP3A4 enzymes since there was no significant effect observed on the pharmacokinetics of midazolam and on the formation of its active metabolite (1-hydroxymidazolam) when midazolam was administered prior to and after a 14-day regimen of tafamidis. The overall systemic exposure ($AUC_{0\text{-}inf}$) and total clearance (CL/F) of midazolam were shown to be equivalent on Day 1 as well as on Day 15 after single dose administrations of midazolam alone and concomitant with steady-state tafamidis.

Summary of Pharmacokinetic Results (Study Fx1A-109)				
Means, Ratio of Means, and 90% Confidence Intervals N=16				
Parameter (units)	**Midazolam Alone (Day 1)**	**Midazolam + Tafamidis (Day 15)**	**% Ratio Day1/Day15**	**90% CI**
Geometric Mean $AUC_{0\text{-}inf}$ (ng·hr/mL)	79.56	73.63	108.07	(100.87, 115.78)
Least Squares Mean CL/F (mL/hr)	97343.20	104345.55	93.29	(86.30, 100.28)

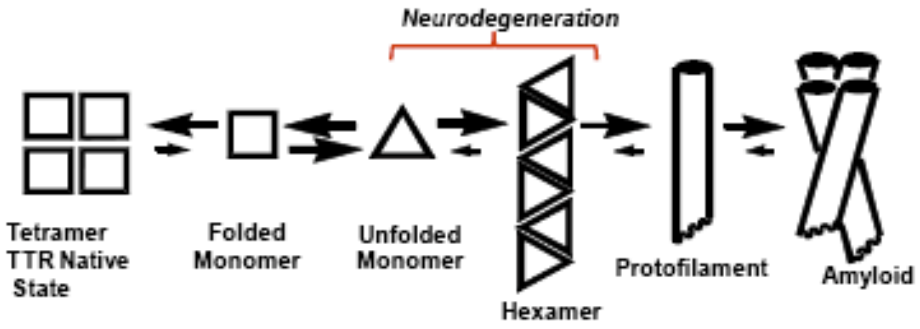
2.4.3. Pharmacodynamics

Mechanism of action

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

Dissociation of the TTR tetramer to monomers is the rate-limiting step in the pathogenesis of TTR amyloidosis. The folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments and ultimately, amyloid fibrils (see fig. 1.1). All disease-associated mutations characterized so far destabilize the TTR tetramer and many influence the velocity of rate-limiting tetramer dissociation.

Figure 1. TTR Amyloid Cascade



Primary and Secondary pharmacology

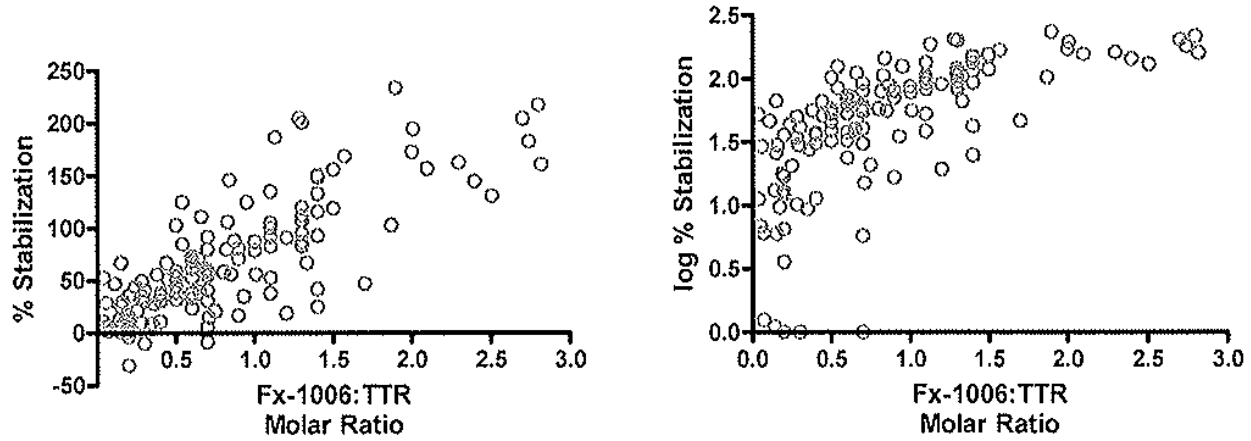
Four PK/PD studies evaluating stabilisation of TTR in the plasma of healthy volunteers after receiving tafamidis or placebo were conducted: study Fx-002, a single and multiple dose escalating study; study Fx-003, a study of food interaction with a single 20 mg dose; study Fx-004, comparing tafamidis administered in a solution with a soft gelatine capsule formulation and study Fx1A-105, a PK study of tafamidis administered orally in subjects with hepatic dysfunction.

For each subject in the study, the fraction of initial tetramer concentration (FOI) was determined in duplicate before dosing (FOIbaseline) and at given time-points after dosing (FOIdosed). The percentage stabilisation of TTR tetramer was defined as follows: % stabilisation = [(aveFOIdosed - aveFOIbaseline) / aveFOIbaseline] * 100. Consequently, a % stabilisation of 100% has a twofold increase in the fraction of initial value over baseline and a % stabilisation of 200% has a threefold increase thereof.

In study Fx-002, following single and repeated administration of tafamidis the average percentage of TTR stabilisation in the placebo group varied from -2 to 6 for the first part (single dose) and from -17 to -6 in the second part of the study (multiple doses). Following both single and repeated doses, tafamidis demonstrated a concentration dependent stabilisation of the TTR tetramer. Following a single dose of 20, 60 and 120 mg, the average concentrations of tafamidis achieved in plasma samples at Tmax were 3.7, 9.1 and 14.4 µM, respectively, which resulted in the average percent stabilisation of 69%, 144% and 189% respectively. Following once daily doses of 15, 30 and 60 mg tafamidis meglumine for 14 days, the average concentrations of tafamidis achieved in plasma samples on Day 15 were 3.3, 7.8 and 9.8 µM, respectively, which resulted in the average percent stabilisation of 57%, 100% and 132%, respectively. No stabilisation was observed in the placebo control groups following either single or multiple doses.

A PD assay was performed on the plasma samples obtained in Fx-002. A plateau (range of difference from baseline: 117-234) was reached for the effect of tafamidis on TTR stabilisation above a plasma tafamidis: TTR stoichiometry of 1.2-1.4 see figure 2.

Fig. 2 Percent stabilisation as a function of tafamidis: TTR molar ration in all Fx-002 samples



In study Fx-003, tafamidis demonstrated a concentration dependent stabilisation of the TTR tetramer in both fed and fasted patients. Following a single 20 mg dose as oral solution, the average concentrations of tafamidis achieved in plasma samples at Tmax were 2.7 and 4.0 µM for the fed and the fasted groups, respectively, resulting in the average percent stabilisation of 31% and 51%, respectively.

In the bioequivalence study (Fx-004) tafamidis meglumine demonstrated a concentration dependent stabilisation of the TTR tetramer in all tested groups, ranging from 40 to 77%.

In subjects with moderate hepatic impairment (study Fx1A-105), the mean molar ratio values were higher in subjects with hepatic impairment due to the lower TTR concentrations and the PK values at 24 h were similar: 24h mean tafamidis plasma concentrations following a single 20 mg dose were 624 ng/ml in healthy volunteers and 537 ng/ml in subjects with moderate hepatic impairment. Steady-state 24 h trough concentrations were predicted to be approximately 2.25 µg/ml in healthy subjects and 1.25 µg/ml in subjects with moderate hepatic impairment, representing a 44% decrease in steady-state trough levels of tafamidis.

PD analyses were also conducted during the pivotal phase II/III Fx-005 study in ATTR-PN patients. The PD analysis was performed on plasma samples for 10 patients given a daily oral dose of 20 mg blinded study medication at the following time points: pre-dose (Baseline), 1, 4, and 24 h post dose on the first day of dosing and after 8 weeks daily dosing (steady state; sample drawn at anytime post dose). All six subjects with measurable levels of tafamidis demonstrated stabilisation after 8 weeks daily oral dosing, while none of the four patients without detectable levels of tafamidis demonstrated stabilisation at this time point. Additionally, all patients with measurable levels of tafamidis had a time point on the first day (1, 4 or 24 h after single dose) that showed stabilisation. The average TTR percent stabilisation after 8 weeks daily dosing was -15% in the four patients without detectable levels of tafamidis and 150% in the six patients with measurable levels of tafamidis.

2.4.4. Discussion on clinical pharmacology

In general, the CHMP considered the documentation adequate to characterise the pharmacokinetics of the active substance and the proposed dosage form. An early formulation (hard gelatine capsule) was abandoned during the product development and a new dosage form (soft gelatine capsules) was found to be bioequivalent to an oral solution early in the clinical development, thus allowing performance of the majority of clinical studies with an adequate formulation.

With respect to special populations, the CHMP considered the observations made in patients with renal and hepatic impairment. Based on the findings from the population PK analysis, where the PK estimates indicated no difference in steady-state clearance of tafamidis in patients based on creatinine clearance, the CHMP was of the view that no dosage adjustment in patients with renal impairment was necessary.

Steady-state 24h trough concentrations were predicted to be higher in healthy subjects than in subjects with moderate hepatic impairment. The reduction in trough concentrations of approximately 44% combined with a 50% reduction in TTR level in moderate hepatic impaired subjects translates to a tafamidis:TTR stoichiometry ratio that is within the therapeutic range. The CHMP considered that the key factor in stabilisation of the TTR tetramer is the tafamidis:TTR stoichiometry and not plasma tafamidis concentrations alone. The results suggested that subjects with moderate hepatic impairment would be expected to demonstrate effective stabilisation of the TTR tetramer following chronic dosing with 20 mg once daily.

Findings related to these patient sub-populations are reflected accordingly in section 4.2 of the SmPC as follows: *"No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Tafamidis has not been studied in patients with sever hepatic impairment and caution is recommended"* and in section 5.2 (Special populations).

The CHMP also discussed the difference in tafamidis clearance and predicted Cmax at steady state between subjects below and above 60 years of age (see Results) and, given the adequate non-clinical safety margins and the clinical safety profile in this patient population, was of the view that the

differences seen would not be clinically relevant. Therefore, no dosage adjustment was requested for the elderly as reflected in the SmPC section 4.2.

There is no clinical experience in pregnant women. The CHMP also considered that no information is available on the presence of tafamidis in human breast milk and that risk to the newborns/ infants cannot be excluded. Hence, the CHMP concluded that tafamidis should not be administered during pregnancy or breastfeeding. This is reflected in section 4.6 of the SmPC.

In terms of food effect, the CHMP considered that the 23% to 32.3% difference in Cmax (lower in fed state) could be of significance in a single dose administration; however, for a chronically administered drug it was not likely to have a clinically significant effect. This was further supported by the population PK model showing that the difference between fed and fasted state is only 9% for Cmax and 5% for AUC, and that this difference is unlikely to be clinically relevant. These conclusions are reflected in sections 4.2 and 5.2 of the SmPC.

With respect to pharmacokinetic interactions, *in vitro* there was evidence that tafamidis is not an inhibitor of the usual CYP450 isozymes CYP1A2, CYP2B6, CYP3A4, CYP2C9, CYP2C19, and CYP2D6. The equivocal induction potential for CY3A4 in vitro prompted an in vivo study. No effects on the PK of the probe drug (midazolam), whether induction or inhibition, were observed in this study. Since the only metabolic pathway identified for tafamidis is glucuronidation, the CHMP concluded that no interaction of potential inhibitors or inducers of CYP450 isozymes on tafamidis PK would be expected.

Pharmacodynamic studies were conducted in support of the mechanism of action of tafamidis (TTR stabilisation) and as a step to dose selection. Tafamidis represents a disease modifying approach to the treatment of TTR amyloidosis. No surrogate markers of clinical efficacy exist to allow short-duration dose-ranging studies. The CHMP considered that the traditional dose findings studies are very difficult to perform, particularly in this orphan condition with a limited patient population. A PK/PD approach was followed to select a dose sufficient to reach the plateau for optimum inhibition of TTR tetramer dissociation.

Stabilization of the wild-type TTR tetramer from healthy volunteers orally dosed with different doses of tafamidis was observed in both single and multiple dose regimens. The stabilization effect reached a plateau above a plasma tafamidis: TTR stoichiometry of 1.2-1.4. This ratio was obtained with a 20 mg dose of tafamidis. The data were considered supportive of the mode of action and dose selection by the CHMP.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted are considered satisfactory.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies were performed. The dose was selected based on pharmacodynamic studies and extrapolated pharmacokinetic data showing that a dose of 20 mg resulted in sufficient plasma concentrations to stabilise transthyretin (1.2 – 2.7 µg/ml). (See Clinical Pharmacology).

2.5.2. Main study

The applicant conducted a single pivotal study Fx-005: safety and efficacy of orally administered tafamidis in patients with familial amyloid polyneuropathy (FAP): a phase II/III, randomised, double-blind, placebo-controlled study.

Methods

Study Participants

Study Fx-005 was conducted at 8 investigational sites, at least one patient was enrolled in each site. The sites were located in France, Portugal, Germany, Spain, Sweden, Argentina and Brazil.

To be eligible to participate in the study, the subjects had to be between 18-75 years old, inclusive. Female patients had to be post-menopausal, surgically sterilised or willing to use two acceptable methods of birth control throughout the study and for three months from the end of the study, male patients with a female partner of childbearing potential had to be willing to use two acceptable methods of birth control for the duration of the study for at least three months from the end of the study. The inclusion criteria further comprised presence of amyloid documented by biopsy, V30M TTR mutation and peripheral and/or autonomic neuropathy with a Karnofsky Performance Status ≥50. Patients were not eligible for entry into the study if they met any of the following criteria: chronic use of NSAIDs other than those allowed by the protocol (ASA, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam and sulindac), primary amyloidosis, pregnancy or breastfeeding, prior liver transplantation, no recordable sensory threshold for vibration perception in both feet, positive results for hepatitis B and/or hepatitis C and/or HIV, renal insufficiency as defined by creatinine clearance <30ml/min, liver function test abnormalities: ALT and/or AST >2 times the upper limit of normal, NYHA functional classification of ≥3, co-morbidity anticipated to limit survival to less than 18 months, investigational drug/device and/or participation in another clinical trial within 60 days before baseline, other causes of sensorimotor neuropathy.

Treatments

All patients received daily a single oral dose of 20 mg tafamidis meglumine (soft gelatine capsule) or matching placebo for a period of 18 months. The following medication was prohibited during the study: any investigational drug within 60 days before baseline through eighteen months of study participation, chronic use of NSAIDs (with the exception of ibuprofen and nimesulid). Liver transplantation was not allowed during study participation, patients undergoing liver transplantation were to be withdrawn from the study.

Objectives

The primary objectives of the study were to evaluate the effect of tafamidis on disease progression in patients with familial amyloid polyneuropathy (FAP) and to evaluate the safety and tolerability of its chronic administration in these patients. The secondary objectives of this study were to determine the pharmacodynamic stabilization effect of tafamidis on human V30M TTR and to determine the population pharmacokinetics in patients with FAP.

Outcomes/endpoints

The co-primary efficacy endpoints of this study were:

• Response to treatment at month 18, as indicated by either improvement (decrease from baseline) or stabilization (change from baseline of 0 to <2) in the Neurologic Impairment Score–Lower Limb (NIS-LL) score

The NIS-LL score for each study visit was based on the average of two scores taken within a one-week period. The NIS-LL was assessed at baseline and at months 6, 12 and 18. For each patient, the rating was performed by the same neurologist throughout the course of the study whenever possible. The NIS-LL composite score ranges from 0 [normal] to 88 [total impairment].

Patients with no disease progression (i.e. improvement or stabilization) were considered responders, patients with disease progression or patients discontinuing their participation prior to month 18 due to liver transplantation or death were considered to be non-responders.

• Change from Baseline to 18 months in the Total Quality of Life score, as measured by the Norfolk QOL-DN

The Norfolk QOL-DN questionnaire was assessed at baseline and at months 6, 12, and 18. The questionnaire consisted of 35 scored items arranged thematically into five domains: physical functioning/large fiber neuropathy, activities of daily living (ADL), symptoms, small fibre neuropathy, and autonomic neuropathy. The total quality of life (TQOL) score was the sum of all five domains (35 questions), with a range of -2 to 135.

The major secondary efficacy endpoints of this study were:

• Change from baseline to months 6, 12, and 18 in NIS-LL

• Change from baseline through month 18 in Sum 7 composite score as measured by nerve conduction studies (NCS), vibration detection threshold (VDT) and heart rate response to deep breathing (HRDB) (i.e. assessment of large fiber function)

• Change from baseline through month 18 in heat pain and cooling thresholds as measured by Quantitative Sensory Testing (QST) utilizing CASE IV (i.e. assessment of small fiber function)

• Change from baseline through month 18 in the modified Body Mass Index (mBMI)

• TTR stabilisation through Month 18 as measured by a validated immunoturbidimetric stabilisation assay

Sample size

The sample size for the trial was based on the need to assess a treatment group effect whereby tafamidis demonstrated superiority over placebo. The sample size was based on the co-primary endpoints of: 1) the categorical response to treatment after 18 months of therapy in the NIS-LL; and 2) the change from baseline to month 18 in the TQOL score as measured by the Norfolk QOL-DN. For the NIS-LL categorical responder analysis, assuming a significance level of 0.05 (2-sided), the power of the test of 90%, response rates of 20% for placebo and 50% for tafamidis, a sample size of 58 per treatment arm was required to achieve statistical significance. For the Norfolk QOL-DN (TQOL), 58 patients per group provided at least 90% power to detect a true difference of 0.6 SD between the groups with a significance level of 0.05 (2-sided), where SD was the square root mean squared error of the ANCOVA model for change from baseline scores. A 5 to 10% dropout rate was assumed.

Therefore, the sample size required for this study was increased to 61-64 patients per arm to accommodate for a loss to follow-up.

Randomisation

All patients were randomly assigned in a 1:1 ratio, in randomisation blocks of four, to receive either the tested drug or matching placebo. Interactive voice response system (IVRS) was used to randomise patients to treatment and to assign study identification numbers. The centralized randomisation was stratified by centre.

Blinding (masking)

The study was conducted in a double-blind fashion. Both tafamidis and placebo were supplied as opaque oblong soft gelatin capsules, identical in appearance; packaging of study medication ensured blinding was maintained for both study participants and investigational staff.

Statistical methods

The following populations were analysed in study Fx-005:

The Intent-to-Treat (ITT) Population was defined as all randomised patients who received at least one dose of study medication (tafamidis or placebo) and who had at least one post baseline efficacy assessment for both the NIS-LL and the Norfolk QOL-DN or who discontinued study due to death or liver transplantation.

The Efficacy Evaluable Population comprised all ITT patients who had non-missing Month 18 NIS-LL and TQOL scores, who took at least 80% of the prescribed study medication and who had no major protocol violations that may have impacted the assessment of efficacy. The co-primary efficacy analysis was conducted on the Efficacy Evaluable Population, as supportive assessments of the ITT co-primary outcomes.

The Safety Population comprised all randomised patients who received at least one dose of study medication (tafamidis or placebo). All safety analyses were conducted on the Safety population.

The primary analysis of the co-primary efficacy endpoints and the pre-specified secondary analysis - a sensitivity analysis of the NIS-LL in which response was imputed for patients who underwent liver transplantation were based on the ITT population. The pre-specified secondary analysis – an analysis in patients with non-missing NIS-LL and TQOL scores at Month 18 and no major protocol violations was based on the Efficacy Evaluable Population.

Superior treatment efficacy of tafamidis compared to placebo was demonstrated if statistically significant (2-sided; alpha of 0.05) treatment differences favouring tafamidis were demonstrated for each of the co-primary endpoints. The co-primary efficacy analyses were:

Neuropathy Impairment Score – Lower Limb (NIS-LL) response to treatment at month 18: a Chi-square test for proportions was used to compare NIS-LL response rates between treatment groups. For patients with post-baseline NIS-LL assessments but no assessment at Month 18, the last observation carried forward (LOCF) method was used to impute missing data at Month 18. Patients who discontinued prior to the 18-month time point due to liver transplantation or death were categorized as non-responders in the primary analysis of NIS-LL.

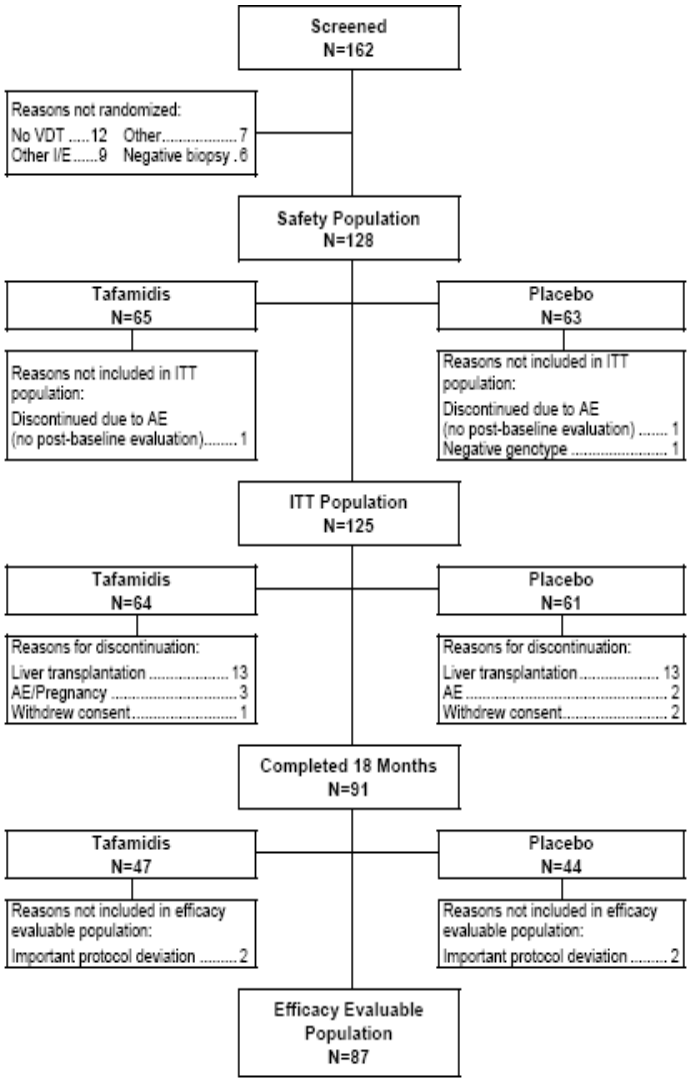
Change from baseline to 18 months in the Total Quality of Life (TQOL) score as measured by the Norfolk Quality of Life – Diabetic Neuropathy (QOL-DN) Questionnaire: an analysis of covariance (ANCOVA) with baseline as covariate was used to compare TQOL scores between treatment groups. For patients with post-baseline Norfolk QOL-DN assessments but no assessment at month 18, LOCF was used to impute missing data at Month 18. For patients without post-baseline Norfolk QOL-DN assessments, the mean change from baseline at Month 18 for patients who had post-baseline assessments was used to impute the change from baseline within each treatment group.

Results

Participant flow

The study participant flow is shown in the figure 3:

Fig.3



VDT=vibration detection threshold; I/E = inclusion/exclusion criteria; AE = adverse event.

Patient completion rate and reasons for discontinuation are presented in table 12.

Table 12

	Number (%) of patients	
	Tafamidis (N=65)	Placebo (N=63)
Total patients completing study	**47 (72.3)**	**44 (69.8)**
Total patients discontinued from study	**18 (27.7)**	**19 (30.2)**
Reason for discontinuation		
Adverse event	4 (6.2)	3 (4.8)
Patient withdrew consent	1 (1.5)	2 (3.2)
Negative genotype	0	1 (1.6)
Liver transplantation	13 (20.0)	13 (20.6)

Study completion rates and reasons for premature discontinuation were similar between the treatment groups. The incidence of liver transplant was the same between both groups. The majority of patients (19 of 26) underwent liver transplantation prior to the 12-month assessment. Most patients enrolled were already on liver transplant lists and the time to transplant was similar between the treatment groups; the proportion of patients on the liver transplant list at the time of enrolment was 71% (46/65) in the tafamidis group and 67% (42/63) of patients in the placebo group. There did not appear to be any association between treatment group and the time to liver transplant in this study.

Recruitment

162 subjects were screened across nine investigational centers; 34 subjects were considered screen failures and 128 subjects were randomized in eight of these centres and were treated with at least one dose of study medication. The first patient was randomized (enrolled) in the study on 16 Jan 2007; the last patient was randomized on 12 Dec 2007. The last double-blind phase patient study visit was on 26 May 2009.

Conduct of the study

The important protocol violations and deviations were observed in four patients treated with tafamidis and 6 patients on placebo and comprised low compliance rate, receipt of wrong drug kit (i.e. incorrect study medication), pregnancy, negative amyloid biopsy and negative genotype. Patients with major protocol deviations were excluded from the efficacy evaluable population (two patients with negative amyloid biopsies, one patient who received wrong medication and one pregnant patient).

The original study protocol Fx-005 was dated 10 August 2006. There were seven global amendments and four country-specific (Germany) amendments. There were a few minor changes made to the analysis from the pre-specified SAP; the SAP was finalized and approved prior to unblinding the study treatment allocation codes. These post hoc efficacy analyses were performed after data availability and unblinding in order to better understand study results. A number of additional safety analyses were not pre-specified in the final SAP (Version 2.0). These post hoc safety analyses were performed to further evaluate the safety profile of tafamidis.

No GCP inspection was conducted.

Baseline data

A summary of demographics and baseline disease characteristics for the ITT population is presented in table 13.

Table 13

	Tafamidis 20 mg N=64	Placebo N=61	p-value[1]
Age, years			
Mean (SD)	39.8 (12.7)	38.4 (12.9)	
Median	35.5	34.0	
Range	25, 74	22, 71	0.339
Age group, n (%)			
≤65 yr	59 (92.2)	58 (95.1)	
>65 yr	5 (7.8)	3 (4.9)	0.510
Gender, n (%)			
Female	32 (50.0)	35 (57.4)	0.410
Race, n (%)			
Caucasian	56 (87.5)	54 (88.5)	
Latin American	6 (9.4)	6 (9.8)	
Not available	2 (3.1)	1 (1.6)	0.736
mBMI at screening			
Mean (SD)	1004.59 (165.2)	1011.54 (212.9)	
Median	974.7	983.8	
Range	655.1, 1510.4	533.3, 1581.5	0.739
Height, cm			
Mean (SD)	166.8 (10.1)	166.6 (11.2)	
Median	167.0	165.5	
Range	147, 186	149, 191	0.843
Weight, kg			
Mean (SD)	64.1 (11.9)	63.9 (13.4)	
Median	62.0	64.0	
Range	39, 91	32, 100	0.962
Baseline NIS-LL (scale 0 to 88)			
Mean (SD)	8.4 (11.4)	11.4 (13.5)	
Median	4.0	6.0	
Range	0, 54	0, 57	0.089
Baseline TQOL (scale -2 to 138)			
Mean (SD)	27.3 (24.2)	30.8 (26.7)	
Median	19.0	22.0	
Range	-1, 110	0, 107	0.401
Duration of symptoms, months			
Mean (SD)	47.0 (48.4)	34.7 (32.9)	
Median	28.0	21.0	
Range	3, 268	2, 133	0.319

[1] P-values based on Wilcoxon's rank sum test for continuous variables and Cochran-Mantel-Haenszel test for categorical variables.

Baseline characteristics were also examined for a subgroup of patients (N=13 in each treatment group) who underwent liver transplantation. While there were no statistically significant differences between the treatment groups for any baseline characteristic in this subgroup, median symptom duration in transplant patients was longer (medians of 57.9 and 34.5 months in the tafamidis and placebo groups, respectively). Consistent with this observation, transplant patients had higher baseline NIS-LL scores (median of 10.0) than non-transplant patients (medians of 4.0).

The ATTR-PN-related medical histories were similar between the treatment groups. The ATTR-PN related medical histories are summarized in table 14. Most patients had both peripheral and autonomic

neuropathy disorders reported in their medical histories (tafamidis: 73.4%; placebo: 82.0%). Approximately 20% of patients experienced only peripheral neuropathy disorders (23.4%; and 18.0%, respectively). Few patients experienced only autonomic neuropathy disorders (3.1% and 0.0%, respectively).

Table 14

Most Common (≥10% of Patients in Either Group) ATTR-PN-related Medical History Preferred Terms (ITT Population) (Study Fx-005)

Preferred Term[1]	Tafamidis 20 mg N=64 n (%)	Placebo N=61 n (%)	All Patients N=125 n (%)
Paresthesia	40 (62.5)	41 (67.2)	81 (64.8)
Weight decreased	23 (35.9)	22 (36.1)	45 (36.0)
Neuralgia	21 (32.8)	20 (32.8)	41 (32.8)
Early satiety	17 (26.6)	14 (23.0)	31 (24.8)
Constipation	15 (23.4)	18 (29.5)	33 (26.4)
Hypoesthesia	15 (23.4)	14 (23.0)	29 (23.2)
Sensory loss	15 (23.4)	15 (24.6)	30 (24.0)
Diarrhea	12 (18.8)	14 (23.0)	26 (20.8)
Anorexia	12 (18.8)	8 (13.1)	20 (16.0)
Urinary retention	10 (15.6)	4 (6.6)	14 (11.2)
Orthostatic hypotension	8 (12.5)	8 (13.1)	16 (12.8)
Dizziness	8 (12.5)	15 (24.6)	23 (18.4)
Gastrointestinal motility disorder[2]	7 (10.9)	12 (19.7)	19 (15.2)
Nausea	7 (10.9)	11 (18.0)	18 (14.4)
Vomiting	7 (10.9)	9 (14.8)	16 (12.8)
Fatigue	7 (10.9)	6 (9.8)	13 (10.4)
Pain in extremity	7 (10.9)	6 (9.8)	13 (10.4)
Neuropathy peripheral	7 (10.9)	7 (11.5)	14 (11.2)
Muscular weakness	6 (9.4)	8 (13.1)	14 (11.2)
Erectile dysfunction	6 (9.4)	8 (13.1)	14 (11.2)

[1] Preferred terms were coded using MedDRA v.10. Patients with multiple preferred terms were counted only once.

[2] Preferred term codes to alternating diarrhea and constipation.

Numbers analysed

Definitions of the ITT, Efficacy Evaluable and Safety populations are provided in section "Statistical methods". Table 15 below summarises numbers analysed within each of the populations.

Table 15

	Tafamidis (N=65) n (%)	Placebo (N=63) n (%)	Total (N=128) n (%)
Intent-to-Treat (ITT) Population	64 (98.5%)	61 (96.8%)	125 (97.7%)
Efficacy Evaluable Population	45 (69.2%)	42 (66.7%)	87 (68%)
Safety Population	65 (100%)	63 (100%)	128 (100%)

Outcomes and estimation

Results obtained on the two co-primary criteria (NIS-LL responders and TQOL) for the ITT primary analysis are presented in table 16 below.

Table 16

Descriptive statistics and estimate variability	Treatment group	Tafamidis	Placebo
	Number of subjects	64	61
	NIS-LL Number (%) of responders	45.3%	29.5%
	95% CI	33.1%;57.5%	18.1%; 41.0%
	TQOL Mean change from baseline Median LSMean (SE)* 95% CI	2.4 1.0 2.0 (2.3) -2.6;6.6	6.9 6.0 7.2 (2.4) 2.6;11.9
Effect estimate per comparison	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.0682
	TQOL	Comparison groups	Tafamidis vs placebo
		P-value	0.1157

*Baseline Least Square Mean (standard error)

Neuropathy Impairment Score – Lower Limb (NIS-LL)

Higher scores on the NIS-LL indicate more pronounced impairment, i.e. increase from baseline in the score reflects a worsening in impairment. Responders versus non-responders were defined with respect to change on the NIS-LL score, worsening ≥2 units being the cut-off for non-responders. This worsening in the NIS-LL was pre-defined as clinically meaningful. At the primary timepoint (Month 18), 45.3% of patients in the tafamidis group had an increase in the NIS-LL of <2, compared to 29.5% patients in the placebo group, but the differences between groups were not statistically significant (p=0.068).

Norfolk QOL-DN (total quality of life, TQOL)

Higher scores on the Norfolk QOL-DN TQOL indicate worse quality of life, i.e. increases from baseline in the score reflect a worsening in quality of life. The placebo-treated patients in the ITT population had progressively worse TQOL scores than tafamidis-treated patients, but the differences between groups were not statistically significant (7.2 versus 2.0, p-value=0.1).

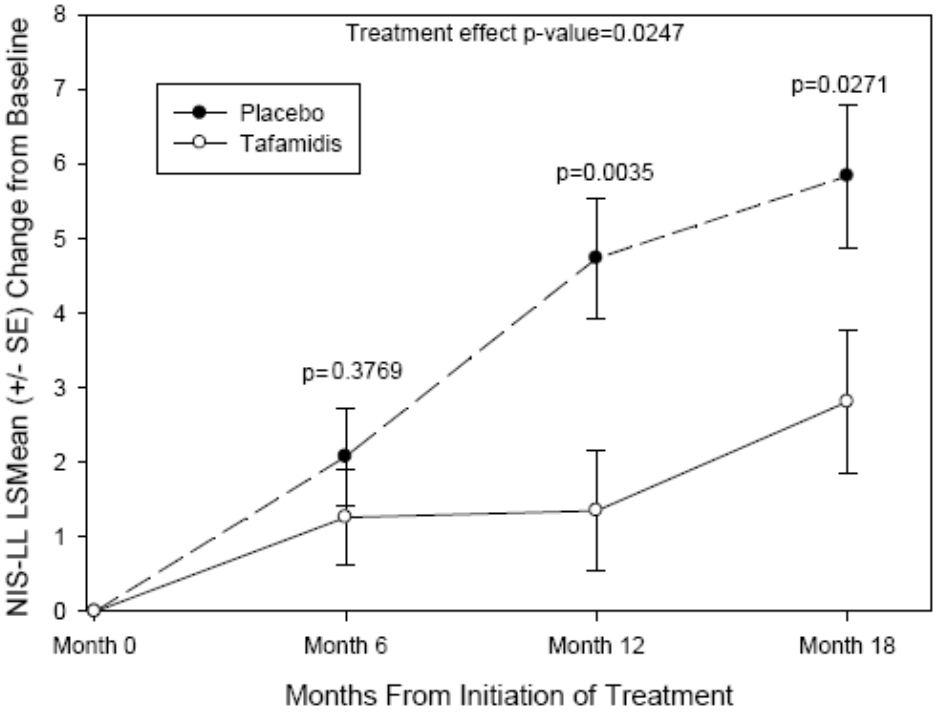
These results are reflected in section 5.1 of the SmPC.

Secondary endpoints

NIS-LL changes from baseline to on-treatment visits

In addition to the categorical analysis of the NIS-LL, a continuous change from baseline analysis was performed. Figure 4 provides a descriptive presentation (LSMeans +SE) of the NIS-LL change scores over time for each treatment group, including assessment at the month 18 primary time point. This analysis provides a picture of the time-course of the treatment effect.

Figure 4

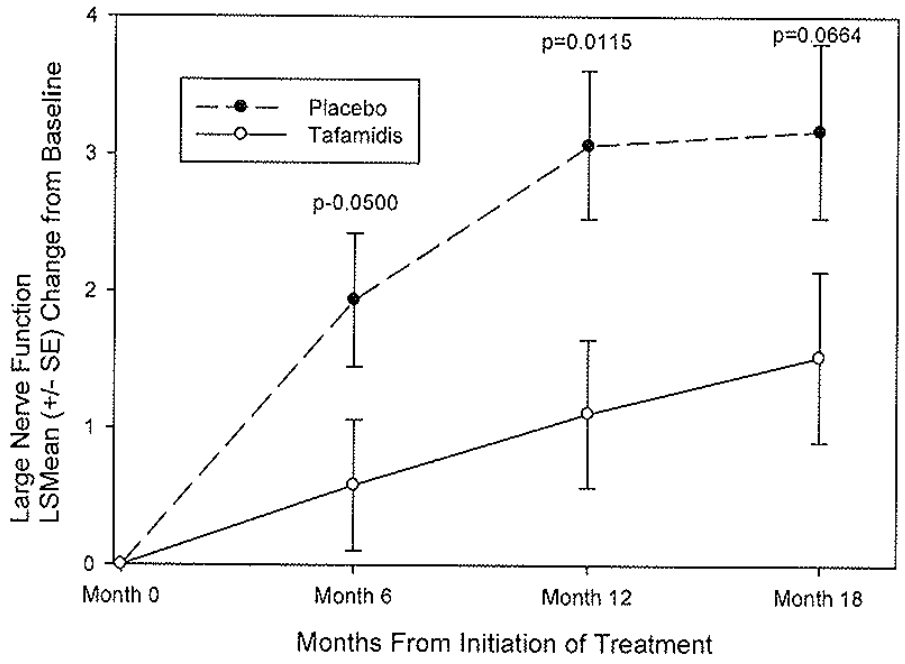


Over the 18-month treatment period, the tafamidis group demonstrated significantly less average worsening of impairment (as measured by LSMean changes in the NIS-LL) compared to the placebo group (overall treatment effect p-value=0.0247), with the differences statistically significant by month 12. By month 18, the LSMean (SE) difference in NIS-LL between the placebo group and the tafamidis group was 3.024 (1.351), 95%CI (-5.699, -0.348), p-value=0.0271. Of note, the CHMP considered that the relevant analysis for this endpoint is the "Primary Imputation Results for NIS-LL Change from Baseline Analysis" (presented in section Ancillary analyses, table 21).

Large fibre function

Composite scores of large fiber function (nerve conduction, vibration threshold and heart rate response to deep breathing – HRDB) were examined over the 18-month treatment period. The LSMean changes from baseline to on-treatment time points for large fiber function are shown in figure 5 below. The outcomes indicated that worsening in large fibre function over 18 months was approximately 50% slower in the tafamidis group than in the placebo group.

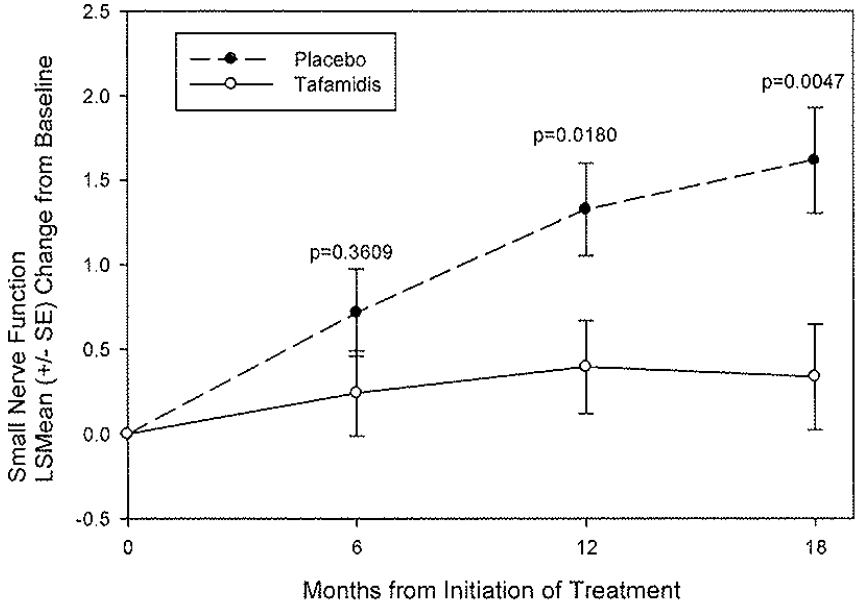
Fig. 5 Large Fiber Function LSMean (SE) Change from Baseline to On-Treatment Visits - Σ7 NTs nds (ITT Population, Observed Case) (Study Fx-005)



Small fibre function

With respect to small fiber function, the treatment group differences also became apparent as early as the 6 month study visit (see fig.6). The outcomes indicate that worsening in small fibre function over 18 months was approximately 80% slower in the tafamidis group than in the placebo group.

Fig. 6 Small Fibre Function LSMean (SE) Change from Baseline to On-Treatment Visits - Σ3 NTSF nds Over Time (ITT Population, Observed Case) (Study Fx-005)



Modified body mass index (mBMI)

Over the course of the 18-month treatment period, patients treated with placebo experienced an average reduction in their mBMI at each on-treatment study visit; in contrast, patients treated with tafamidis experienced an average increase in their mBMI at each on-treatment study visit (by 18 months, there was a 73.1-point difference between the tafamidis (LSMean [±SE] change from baseline of 39.3±11.5) and placebo (-33.8±11.8) groups. The placebo group demonstrated an average worsening in mBMI while the tafamidis group demonstrated an average improvement in mBMI; these differences between the treatment groups were statistically significant (p-value<0.0001). The CHMP considered that there might be limitations to interpreting the mBMI changes, but was of the view that this criterion is easily measurable and might be of interest to evaluate progression of the disease, particularly the nutritional status.

Results of the major secondary endpoints (NIS-LL change from baseline, large fibre change from baseline, small fibre change from baseline and mBMI change from baseline) are reflected in section 5.1 of the SmPC.

TTR stabilisation

TTR stabilization (as defined by the TTR stabilization assay) was observed in 97.9% of patients on tafamidis and in no patients on placebo at 18 months. Most patients with stabilized TTR had measureable concentrations of tafamidis.

The TTR stabilisation status of the population at different time points is presented in table 17 below.

Table 17

TTR Stabilization Status (ITT Population) (Study Fx-005)

		Tafamidis 20 mg N=64	Placebo N=61	Tafamidis vs. Placebo
Week 8	# Stabilized/# Observations (%)	62/63 (98.4)	4/60 (6.7)	
	95% confidence interval	95.3%, 100%	0.4%, 13.0%	
	p-value[1]			<0.0001
Month 6	# Stabilized/# Observations (%)	59/59 (100)	3/58 (5.2)	
	95% confidence interval	100%, 100%	0.0%, 10.9%	
	p-value[1]			<0.0001
Month 12	# Stabilized/# Observations (%)	47/48 (97.9)	1/50 (2.0)	
	95% confidence interval	93.9%, 100%	0.0%, 5.9%	
	p-value[1]			<0.0001
Month 18	# Stabilized/# Observations (%)	47/48 (97.9)	0/44 (0.0)	
	95% confidence interval	93.9%, 100%	0.0%, 0.0%	
	p-value[1]			<0.0001

[1] Based on Chi-square test for proportions.

Ancillary analyses

The majority of patients enrolled into this study were on a liver transplant list. Liver transplantation in this patient population is performed as early as possible in the course of the disease when an organ match becomes available. The time to event analysis suggested that patients in both treatment groups who underwent liver transplantation in the trial did so not because of disease progression or as

"salvage" therapy, but when a match was available, and thus categorizing liver transplant patients as non-responders in the primary analysis of the NIS-LL was a conservative statistical approach (i.e. a worst-case analysis). With that consideration, the statistical plan pre-specified a secondary sensitivity analysis imputing the effect of liver transplantation on the NIS-LL response.

Results of this sensitivity analysis are presented in table 18 below:

Table 18

Descriptive statistics and estimate variability	Treatment group	Tafamidis	Placebo
	Number of subjects	64	61
	NIS-LL Number (%) of responders	54.7%	36.1%
	95% CI	42.5%; 66.9%	24.0%; 48.1%
	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.0367

As requested by the CHMP, the applicant also provided additional analyses regarding the NIS-LL responders (table 19 and 20) as well as the mean NIS-LL change from baseline (tables 21 and 22). The analyses were based on multiple imputation and missing values imputed according to their respective treatment group or according to placebo (see Discussion).

Table 19
Primary Multiple Imputation Results for NIS-LL Responder Analysis

Multiple Imputation Batch Run*	Efficacy Estimate	Standard Error	Confidence Interval	p-value
1	0.146	0.095	-0.041, 0.332	0.125
2	0.144	0.095	-0.042, 0.331	0.130
3	0.146	0.095	-0.041, 0.333	0.125

* Each batch run represents the results combined from 1000 multiply imputed data sets.

Table 20
Sensitivity Multiple Imputation Results for NIS-LL Responder Analysis, All Missing Values Imputed Using Placebo Model

Multiple Imputation Batch Run*	Efficacy Estimate	Standard Error	Confidence Interval	p-value
1	0.139	0.094	-0.046, 0.324	0.140
2	0.138	0.094	-0.046, 0.323	0.142
3	0.139	0.095	-0.046, 0.325	0.141

* Each batch run represents the results combined from 1000 multiply imputed data sets.

Table 21
Primary Imputation Results for NIS-LL Change from Baseline Analysis

Multiple Imputation Batch Run*	Efficacy Estimate	Standard Error	Confidence Interval	p-value
1	-2.787	1.345	-5.423, -0.151	0.041
2	-2.815	1.351	-5.464, -0.166	0.040
3	-2.798	1.347	-5.438, -0.157	0.040

* Each batch run represents the results combined from 1000 multiply imputed data sets.

Table 22
Sensitivity Multiple Imputation Results for NIS-LL Change from Baseline Analysis, All Missing Values Imputed Using Placebo Model

Multiple Imputation Batch Run*	Efficacy Estimate	Standard Error	Confidence Interval	p-value
1	-2.310	1.429	-5.112, 0.491	0.109
2	-2.333	1.427	-5.130, 0.464	0.105
3	-2.319	1.429	-5.119, 0.481	0.108

Each batch run represents the results combined from 1000 multiply imputed data sets.

Results in the Efficacy Evaluable Population, i.e. from a pre-specified secondary analysis in patients with non-missing NIS-LL and TQOL scores at Month 18 and no major protocol violations are presented in table 23 below.

Table 23

Descriptive statistics and estimate variability	Treatment group	Tafamidis	Placebo
	Number of subjects	45	42
	NIS-LL Number (%) of responders	60.0%	38.1%
	95% CI	45.7%; 74.3%	23.4%; 52.8%
	TQOL LSMean (SE)*	0.1 (3.0)	8.9 (3.1)
	95% CI	-5.8, 6.0	2.8, 15.0
Effect estimate per comparison	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.04
	TQOL	Comparison groups	Tafamidis vs placebo
		P-value	0.045

*Baseline Least Square Mean (standard error)

In the efficacy evaluable population, assessment of the NIS-LL response at Month 18 demonstrated that 60.0% of patients in the tafamidis group had no disease progression at Month 18, compared to 38.1% patients in the placebo group (p=0.04). The results for TQOL for the efficacy evaluable population were also statistically significant at 18 months (0.1 in the tafamidis group versus 8.9 in the placebo group, p=0.045).

These results are reflected in section 5.1 of the SmPC.

Summary of the main study

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

Table 24 Summary of Efficacy for trial Fx-005

Title: Safety and Efficacy of Orally Administered Tafamidis (Fx-1006A) in Patients with Familial Amyloid Polyneuropathy (FAP): A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study			
Study identifier	Fx-005		
Design	Multicenter, Randomized, Double-Blind, Placebo-Controlled Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18 months Not applicable Not applicable (extension study Fx-006 – 12 months)
Hypothesis	Superiority		
Treatments groups	Tafamidis		Tafamidis 20 mg (1 capsule) once daily for 18 months; number of randomized patients: 65
	Placebo		Matching placebo once daily for 18 months; number of randomized patients: 63
Endpoints and definitions	Co-Primary endpoint	NIS-LL	Neuropathy Impairment Score – Lower Limb (NIS-LL) response to treatment at Month 18. Responders were defined as patients with no disease progression as measured by an increase from baseline in NIS-LL of less than 2 points.
	Co-Primary endpoint	TQOL	Change from baseline to 18 months in the Total Quality of Life (TQOL) score as measured by the Norfolk Quality of Life – Diabetic Neuropathy (QOL-DN) Questionnaire.
Database lock	30 June 2009		
Results and Analysis			
Analysis description	**Primary Analysis of the co-primary endpoints**		
Analysis population and time point description	Intent-to-Treat (ITT) – all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment for both NIS-LL and Norfolk QOL-DN or discontinued the study due to death or liver transplant. Both co-primary endpoints were evaluated in the ITT population using the last observation carried forward (LOCF) to impute missing data at Month 18. Analysis of both variables at the Month 18 time point.		
Descriptive statistics and estimate variability	Treatment group	Tafamidis	Placebo
	Number of subjects	64	61
	NIS-LL Number (%) of responders	45.3%	29.5%
	95% CI	33.1%;57.5%	18.1%; 41.0%

	TQOL Mean change from baseline Median LSMean (SE)* 95% CI	2.4 1.0 2.0 (2.3) -2.6;6.6	6.9 6.0 7.2 (2.4) 2.6;11.9
Effect estimate per comparison	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.0682
	TQOL	Comparison groups	Tafamidis vs placebo
		P-value	0.1157
Notes	-		
Analysis description	**Pre-specified secondary analysis - a sensitivity analysis of the NIS-LL in which response was imputed for patients who underwent liver transplantation**		
Analysis population and time point description	Intent-to-Treat (ITT) – all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment for both NIS-LL and Norfolk QOL-DN or discontinued the study due to death or liver transplant. Analysis at the Month 18 time point.		
Descriptive statistics and estimate variability	Treatment group	Tafamidis	Placebo
	Number of subjects	64	61
	NIS-LL Number (%) of responders	54.7%	36.1%
	95% CI	42.5%; 66.9%	24.0%; 48.1%
Effect estimate per comparison	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.0367
Notes	The majority of patients enrolled into this study were on a liver transplant list. Liver transplantation in this patient population is performed as early as possible in the course of disease when an organ match becomes available. The time to event analysis suggested that patients in both treatment groups who underwent liver transplantation in the current trial did so not because of disease progression or as "salvage" therapy, but when a match was available, and thus categorizing liver transplant patients as non-responders in the primary analysis of the NIS-LL was a very conservative statistical approach (i.e., a worst-case analysis). With that consideration in mind, the statistical plan pre-specified a sensitivity analysis imputing the effect of liver transplantation on the NIS-LL response.		
Analysis description	**Pre-specified secondary analysis - analysis in patients with non-missing NIS-LL and TQOL scores at Month 18 and no major protocol violations (Efficacy Evaluable population)**		
Analysis population and time point description	Efficacy Evaluable population – all ITT patients with non-missing Month 18 NIS-LL and TQOL scores, who took at least 80% of study medication, and had no major protocol violations. Analysis at the Month 18 time point.		
Descriptive statistics and estimate	Treatment group	Tafamidis	Placebo
	Number of subjects	45	42

variability	NIS-LL Number (%) of responders	60.0%	38.1%
	95% CI	45.7%; 74.3%	23.4%; 52.8%
	TQOL LSMean (SE)*	0.1 (3.0)	8.9 (3.1)
	95% CI	-5.8, 6.0	2.8, 15.0
Effect estimate per comparison	NIS-LL	Comparison groups	Tafamidis vs placebo
		P-value	0.04
	TQOL	Comparison groups	Tafamidis vs placebo
		P-value	0.045
Notes			

*Baseline Least Square Mean (standard error)

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

N.A.

Clinical studies in special populations

N.A.

Supportive studies

Fx-006

This was an open-label extension to study Fx-005, of 12-month duration, evaluating long-term safety and clinical outcomes of tafamidis in patients with ATTR-PN.

The objectives of the study were to evaluate the long-term safety and tolerability of chronic administration of tafamidis in patients with ATTR-PN, to evaluate the long-term effects of tafamidis on disease progression in patients with ATTR-PN, to determine the pharmacodynamic (PD) stabilisation effect of tafamidis on human V30M TTR and to obtain additional pharmacokinetic (PK) samples for population PK analysis in this patient population.

Male and non-pregnant female patients who completed the month 18 visit of study Fx-005 were eligible; patients who had undergone liver transplantation could not be enrolled. All patients were treated with a single daily dose of 20 mg tafamidis for 12 months. The treatment groups were identified as "tafamidis-tafamidis" and "placebo-tafamidis", based on their treatment sequence.

Criteria for evaluation used in the study were consistent with those used in the pivotal trial and comprised assessments of NIS-LL (including subscales), NIS-LL responders, TQOL and individual domain scores of Norfolk Quality of Life – DN questionnaire, large fibre function, small fibre function, mBMI. The pharmacodynamic endpoint TTR stabilisation was measured at months 6 and 12 by a validated immunoturbidimetric assay.

The rate of disease progression as measured by the monthly rate of change in the various endpoints during the 12-month treatment (in study Fx-006) was compared with the rates of change during the

first 18 months of treatment (in study Fx-005) for the tafamidis group, i.e. sustainability of treatment effect.

The rate of disease progression during 12 months of tafamidis treatment (in study Fx-006) was compared with the previous rate of change during 18 months of placebo treatment (in study Fx-005) for the placebo-tafamidis group, i.e. "superiority" of treatment effect. Of note, the CHMP argued that due to the design of the study, the analysis should not be considered a superiority analysis.

The change from Fx-005 baseline to the end of study Fx-006 (30 months) was compared between the tafamidis-tafamidis group and the placebo-tafamidis group, i.e. effect of early-start treatment.

The pharmacodynamic analysis (TTR stabilisation) was measured at week 6 and months 6 and 12. The proportion of patients achieving TTR stabilisation and the 95% CI were summarized at each time point.

Results

Following 18 months of placebo treatment in Study Fx-005, at enrolment into the extension Fx-006 patients switching to tafamidis had more severe disease compared to patients who had been previously treated with tafamidis, as evidenced by the statistically significantly worse NIS-LL scores and worse quality of life. The mBMI was also lower for the placebo-tafamidis patients compared to the tafamidis-tafamidis patients, but the difference was not statistically significant. Table 25 summarises the baseline disease characteristics for patient continuing in the Fx-006 extension study.

Table 25

Baseline Disease Characteristics – ITT Population (Study Fx-006)

		Tafamidis-Tafamidis N=38	Placebo-Tafamidis N=33	All Patients N=71	p-value[1]
NIS-LL (scale 0 to 88)					
Fx-005 baseline	Mean (SD)	6.8 (10.0)	11.6 (14.5)	9.0 (12.5)	0.1382
	Median	4.0	6.0	4.0	
	Range	0, 49	2, 57.3	0, 57.3	
Fx-006 baseline	Mean (SD)	8.4 (13.2)	17.5 (20.8)	12.6 (17.7)	0.0145
	Median	5.3	10.0	6.5	
	Range	0, 65	0, 75	0, 75	
Norfolk QOL-DN (TQOL) (-2 to 138)					
Fx-005 baseline	Mean (SD)	21.0 (21.1)	27.1 (24.8)	23.8 (22.9)	0.1808
	Median	14.0	17.0	15.0	
	Range	-1, 110	0, 107	-1, 110	
Fx-006 baseline	Mean (SD)	21.1 (21.9)	38.1 (31.9)	29.0 (28.1)	0.0204
	Median	11.0	28.0	15.0	
	Range	-1, 97	-1, 96	-1, 97	
Large Fiber Function (Σ7 NTs nds)					
Fx-005 baseline	Mean (SD)	5.8 (8.7)	6.8 (8.9)	6.3 (8.8)	0.6242
	Median	3.4	9.5	7.2	
	Range	-8.8, 23.1	-10.6, 20.9	-10.6, 23.1	
Fx-006 baseline	Mean (SD)	6.7 (8.5)	10.1 (10.7)	8.3 (9.7)	0.1849
	Median	5.0	10.8	8.5	
	Range	-6.6, 25.3	-7.3, 25.1	-7.3, 25.3	

Small Fiber Function (Σ3 NTSF nds)					
Fx-005 baseline	Mean (SD)	4.3 (4.2)	5.5 (3.7)	4.8 (4.0)	0.2237
	Median	4.1	5.0	4.4	
	Range	-4.4, 11.2	-1.1, 11.2	-4.4, 11.2	
Fx-006 baseline	Mean (SD)	4.8 (4.3)	7.1 (4.4)	5.8 (4.5)	0.0195
	Median	4.2	7.4	5.5	
	Range	-2.5, 11.2	-2.1, 11.2	-2.5, 11.2	
mBMI					
Fx-005 baseline	Mean (SD)	1031.6 (166.5)	1020.2 (244.3)	1026,3 (204.9)	0.9128
	Median	1015.9	1071.4	1023.8	
	Range	687.9, 1510.4	533.3, 1581.5	533.3, 1581.5	
Fx-006 baseline	Mean (SD)	1068.4 (142.4)	990.1 (265.0)	1032.6 (209.7)	0.0800
	Median	1038.1	945.7	1025.6	
	Range	780.1, 1473.7	567.5, 1583.8	567.5, 1583.8	

Results concerning sustainability of the treatment effect are presented in table 26. Of note, there were no statistically significant differences in the rates of change in NIS-LL and quality of life measurements in the Fx-006 extension study when compared with Study Fx-005. The increase in mBMI over the first 18 months of tafamidis administration was not observed over the last 12 months. There was a decrease in mBMI, translating into a statistically significant difference in the rate of change (p=0.0006). The changes from Fx-005 baseline after 30 months of tafamidis for all endpoints demonstrated less impairment than what was observed after 18 months of placebo.

Table 26

Sustainability of the Treatment Effect: Rate of Change per Month for All Efficacy Endpoints – Efficacy Evaluable Population (Study Fx-006)

	Rate of Change in U/month (SEM)				
	Tafamidis-Tafamidis (N=30)				**Placebo (N=42)**
Endpoint	**Fx-006 (12 months)**	**Fx-005 (18 months)**	**p-value[1]**	**Fx-005/006 (30 months)**	**Fx-005 (18 months)[2]**
NIS-LL	0.07 (0.08)	0.06 (0.06)	0.9638	0.07 (0.04)	0.33 (0.06)
Norfolk QOL-DN (TQOL)	0.13 (0.21)	-0.19 (0.16)	0.1275	-0.08 (0.06)	0.45 (0.17)
Σ7 NTs nds	0.05 (0.05)	0.05 (0.04)	0.9943	0.05 (0.02)	0.17 (0.04)
Σ3 NTSF nds	0.05 (0.03)	0.03 (0.02)	0.3896	0.03 (0.01)	0.09 (0.02)
mBMI	-1.88 (1.10)	1.95 (0.81)	0.0014	0.40 (0.45)	-1.27 (0.67)

1 P-values (comparing the rate of change for the tafamidis-tafamidis group in Study Fx-006 to the rate of change in Study Fx-005) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.
2 ITT patients treated with placebo in Study Fx-005.

Table 27 summarises results concerning "superiority" of the treatment effect. There was a statistically significant difference in the rate of change by month in the NIS-LL, the quality of life and the mBMI over 12 months of tafamidis administration during the Fx-006 extension study compared to the 18 months of placebo treatment in the Fx-005 study.

Table 27

Rate of Change per Month for All Efficacy Endpoints – ITT Population (Study Fx-006)

Endpoint	Rate of Change in U/month (SEM)			
	Placebo-Tafamidis (N=33)			Tafamidis (N=64)
	Fx-006 (12 months)	Fx-005 (18 months)	p-value[1]	Fx-005 (18 months)[2]
NIS-LL	0.16 (0.08)	0.34 (0.06)	0.0103	0.16 (0.05)
Norfolk QOL-DN (TQOL)	-0.16 (0.21)	0.61 (0.16)	0.0003	0.12 (0.15)
Σ7 NTs nds	0.11 (0.05)	0.18 (0.04)	0.2133	0.08 (0.03)
Σ3 NTSF nds	0.04 (0.03)	0.09 (0.02)	0.0551	0.02 (0.02)
mBMI	5.19 (1.13)	-1.77 (0.78)	<0.0001	2.05 (0.61)

1 P-values (comparing the rate of change for the tafamidis-tafamidis group in Study Fx-006 to the rate of change in Study Fx-005) based on a mixed model ANOVA. The dependent variable was the measurement at each visit. The independent variables were the study-by-treatment interaction and the time-by-study-by-treatment interaction. The intercept and time variables were modeled as random effects. The test of treatment effect was based on the time-by-study-by-treatment interaction.
2 Efficacy evaluable patients treated with placebo in Study Fx-005.

Table 28 summarises results on the TTR stabilisation status. TTR stabilization (as defined by the TTR stabilization assay) was observed in 91.4% of patients treated with tafamidis for 30 months (tafamidis-tafamidis patients) and 89.5% of patients on tafamidis for 12 months (placebo-tafamidis patients) at the Month 12 Fx-006 evaluation.

Table 28 TTR stabilisation status – ITT population

		Tafamidis-Tafamidis	Placebo-Tafamidis
Week 6	# Stabilized/# Observations (%)	35/38 (92.1)	30/31 (96.8)
	95% confidence interval	(0.81, 0.99)	(0.83, 0.99)
Month 6	# Stabilized/# Observations (%)	34/37 (91.9)	31/32 (96.9%)
	95% confidence interval	(0.81, 0.99)	(0.83, 0.99)
Month 12	# Stabilized/# Observations (%)	32/35 (91.4)	28/30 (93.3)
	95% confidence interval	(0.80, 0.99)	(0.77, 0.99)

Fx1A-201

This was an open-label, multicentre, single-arm study of tafamidis in ATTR-PN patients with non V30M TTR mutation, evaluating the effects of tafamidis on transthyretin stabilisation and clinical outcome measures in patients with non-V30M transthyretin amyloidosis.

The study was conducted in 2 parts. Part 1 included a 6-week dosing period, during which all enrolled patients received oral tafamidis 20 mg once daily for 6 weeks. At Week 6, blood samples were collected from each patient to determine TTR stabilization. Patients who completed the Week 6 visit

continued receiving daily oral dose of 20 mg for up to a total of 12 months during Part 2 of this study. As planned in the protocol, if it was determined that a patient was not stabilized at Week 6, the patient was to be discontinued from the study.

The primary objective of the study was to determine transthyretin stabilisation at steady state, as measured by a validated immunoturbidimetric assay, in patients with non V30M TTR amyloidosis. The primary and secondary pharmacodynamic endpoints were TTR stabilisation at week 6 compared to baseline as measured by a validated immunoturbidimetric stabilisation assay (ITTSA) and TTR stabilisation at months 6 and 12 compared to baseline, respectively.

The secondary objectives were to evaluate the safety and tolerability of tafamidis in patients with non V30M TTR amyloidosis, to determine plasma concentrations at steady-state time points and to evaluate clinical outcomes in patients with non V30M TTR amyloidosis. The exploratory efficacy endpoints included NIS, NIS-LL, NIS-UL and subscale scores, TQOL, mBMI. Descriptive analyses were performed.

Male and female patients between the ages of 18 and 75 years diagnosed with TTR amyloidosis with documented non-V30M TTR mutation and positive biopsy were eligible for the study. Patients who had undergone liver transplantation could not be enrolled.

Up to 24 patients were planned to be enrolled in this study. A total of 21 patients were enrolled and analyzed. The intent-to-treat (ITT) population consisted of all enrolled patients who received at least one dose of tafamidis meglumine and therefore the ITT and Safety populations for this study are the same.

Results

21 patients were enrolled in this trial, 18 completed it and 3 discontinued early for the following reasons: transient ischemic attack, liver transplant and combined liver/heart transplant.

A summary of the patients´ baseline characteristics is presented in table 29 below.

Table 29

Patient Demographics – ITT Population (Study Fx1A-201)

Demographic	Tafamidis 20 mg (N=21)
Age (year)	
Mean (SD)	63.1 (9.86)
Median	64.3
Range	43.9, 76.8
25th Percentile	56.9
75th Percentile	70.8
Age group, n (%)	
≤ 65 yr	11 (52.4)
> 65 yr	10 (47.6)
Gender, n (%)	
Male	13 (61.9)
Female	8 (38.1)
Race, n (%)	
Afro-Caribbean	1 (4.8)
Asian	1 (4.8)
Caucasian	19 (90.5)

SD = standard deviation

At baseline, patients demonstrated significant neurologic impairment, with a mean NIS total score of 48.7 and a mean NIS-LL total score of 27.6. Disease-specific quality of life was impaired, as evidenced by a mean Norfolk TQOL of 47.8, and so was the functional status (Karnofsky Performance Status Scale mean score of 74.8). However, overall nutritional status was preserved, as evidenced by relatively normal mean mBMI of a 1053.

A review of the ATTR-related medical history demonstrated expected neurologic abnormalities (95.2%), cardiac disorders (57.1%) including cardiac pacemaker insertion (14.3%) arrhythmia (14.3%), cardiac amyloidosis, cardiac failure and cardiac failure congestive (9.5% each), orthostatic hypotension (9.5%), gastrointestinal disorders (52.4%) mainly diarrhoea (23.8%) and musculoskeletal/connective tissue disorders (28.6%).

A summary of the ATTR-related medical history categorised by symptom-classification is presented in table 30.

Table 30

Summary of ATTR-related Medical History Categories by Symptom Classification – ITT Population (Study Fx1A-201)

Symptom Classification	Tafamidis 20 mg (N=21) n (%)
Peripheral neuropathy only	3 (14.3)
Peripheral and autonomic neuropathy	5 (23.8)
Peripheral neuropathy and cardiomyopathy	7 (33.3)
Autonomic neuropathy and cardiomyopathy	1 (4.8)
Peripheral and autonomic neuropathy and cardiomyopathy	5 (23.8)

The results regarding TTR stabilisation (as defined by the TTR stabilization assay) at week 6 and months 6 and 12 are presented in table 31. Treatment with tafamidis over 12 months in a mixed genotype population of patients with ATTR-PN resulted in TTR stabilization in 95% of patients by week 6 and 100% of patients at months 6 and 12, supporting persistence of TTR stabilization with chronic dosing of tafamidis.

Table 31

Transthyretin Stabilization at Week 6 – ITT Population (Study Fx1A-201)

Parameter	Tafamidis 20 mg (N=21)
Week 6 transthyretin stabilization[1]	n=19
Number (%) stabilized	18 (94.7%)
95% confidence interval	74.0%, 99.9%

[1] All patients enrolled who received study medication and had both the baseline and post-baseline TTR stabilization measurements.

Note: Percent calculated based on number of patients providing both baseline and Week 6 data.

TTR Stabilization at Months 6 and 12 – ITT Population (Study Fx1A-201)

Parameter	Tafamidis 20 mg (N=21)
Month 6 TTR Stabilization[1]	n=18
Number (%) stabilized[2]	18 (100.0%)
95% confidence interval	81.5%, 100.0%
Month 12 TTR Stabilization[1]	n=17
Number (%) stabilized	17 (100.0%)
95% confidence interval	80.5%, 100.0%

[1] All patients enrolled who received study medication and had both the baseline and post-baseline TTR stabilization measurements.

[2] Patient 03-003 was not stabilized at Week 6 but was stabilized at Months 3 and 6. He is reflected stabilized at Month 6

TTR = transthyretin

The results regarding NIS, NIS-LL and NIS-UL scores are summarized in table 32. The mean and median scores indicate an impairment of the neurologic function from baseline to month 12. Quality of life (TQOL) remained unchanged over the 12-month period and after a decrease at month 6, a slight improvement in nutritional status (mBMI) was observed at month 12.

Table 32

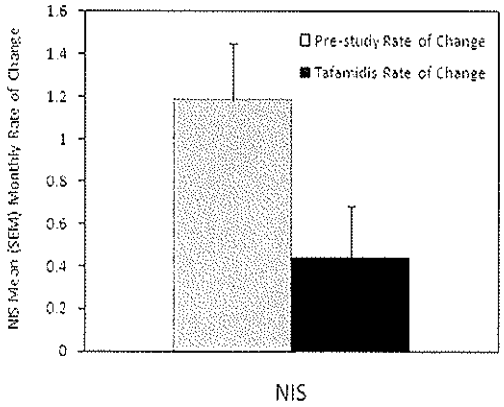
Baseline and Change from Baseline to Months 6 and 12 in NIS, NIS-LL, and NIS-UL Scores – ITT Population (Study Fx1A-201)

Visit	Statistic	NIS[1] (range 0-244)	NIS-LL (range 0-88)	NIS-UL[1] (range 0-156)
Baseline	n	21	21	21
	Mean (SD)	48.7 (44.31)	27.6 (24.67)	21.1 (21.42)
	Median	45.0	18.0	13.0
	Range	0.0, 131.9	0.0, 69.9	0.0, 65.6
	95% CI	28.5, 68.9	16.4, 38.9	11.3, 30.8
Month 6	n	17	19	17
	Mean (SD)	52.3 (49.29)	29.2 (26.10)	24.1 (25.35)
	Median	56.0	26.0	15.0
	Range	0.0, 142.9	0.0, 71.0	0.0, 75.4
	95% CI	26.9, 77.6	16.6, 41.8	11.1, 37.1
Month 6 change from baseline	n	17	19	17
	Mean (SD)	2.0 (9.52)	-0.5 (5.73)	2.0 (5.56)
	Median	3.0	0.0	0.0
	Range	-17.0, 21.5	-11.0, 8.0	-6.0, 16.0
	95% CI	-2.9, 6.9	-3.2, 2.3	-0.8, 4.9
Month 12	n	18	18	18
	Mean (SD)	60.8 (52.13)	34.0 (27.38)	26.8 (26.95)
	Median	57.5	34.8	18.5
	Range	0.0, 154.8	0.0, 75.0	0.0, 80.3
	95% CI	34.9, 86.7	20.4, 47.6	13.4, 40.2
Month 12 change from baseline	n	18	18	18
	Mean (SD)	5.3 (12.62)	2.7 (6.21)	2.5 (7.43)
	Median	1.6	1.0	0.5
	Range	-16.5, 29.5	-10.5, 11.5	-6.0, 18.0
	95% CI	-1.0, 11.5	-0.4, 5.8	-1.2, 6.2

[1] For the NIS and NIS-UL scores, 1 patient (patient 03-002) did not complete Part 1 and 3 patients had missing values at Month 6 (02-005, 03-005, and 03-008). However, patient 03-005 did have Month 6 scores for the NIS-LL.

Furthermore, the applicant also provided comparison between the monthly rates of change on the NIS score before vs after treatment with tafamidis. A slower rate of neurologic disease progression over 12 months of tafamidis administration (NIS=0.4 units/month) was observed as compared with the rate during the pre-study period (1.16 units/month), as shown in figure 7.

Figure 7 Monthly rates of change in NIS prior to enrolment (pre-study) and during treatment with tafamidis



2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

One pivotal phase II/III study (Fx-005) was conducted: safety and efficacy of orally administered tafamidis in patients with familial amyloid polyneuropathy (FAP): randomised, double-blind, placebo-controlled, multicentre international study in patients with ATTR-PN due to V30M mutation. There is no dedicated guideline regarding the condition but the design of the pivotal trial (parallel groups, randomisation, double-blind) is a standard approach to evaluating efficacy. As there is no pharmacological treatment available to treat the disease, use of placebo is considered acceptable. Overall, the CHMP concluded that the design of the pivotal trial was appropriate.

The patient population enrolled in the study is represented by ATTR-PN patients with a V30M mutation, which is the principal mutation seen in these patients. However, ATTR-PN can be linked to other mutations and therefore, validity of data generated in this trial should be interpreted with caution when considering the overall population of ATTR-PN patients. Patients with mutations other than V30M were only included in the open-label Fx1a-201 study. This is discussed further in the sub-section Efficacy data and additional analyses.

The CHMP considered that NIS-LL and TQoL are scores used and validated in diabetic neuropathy and discussed their use as co-primary endpoints in the setting of the ATTR-PN. The observational study Fx1A-OS-001 showed that these scores could discriminate between healthy volunteers and ATTR-PN patients, but with questionable capacity to distinguish different levels of disease progression. The Fx1A-OS-001 study showed differences of mean NIS-LL according to different disease stages, but there was overlap of the values between stages 2 and 3 and uncertain relationship between progression in the NIS score and the disease progression. The CHMP also considered that the familial amyloid polyneuropathy is a length-dependent condition with a pre-dominant progressive sensory loss. On the NIS-LL score, the maximum total score possible for the sensory component is 16/88 points compared to the maximum total score possible for the motor component of 64/88. Since the condition manifests

predominantly a sensory neuropathy, the ability of NIS-LL to properly evaluate disease progression in ATTR-PN was discussed by the CHMP. In order to provide more data on the clinical relevance of the criteria chosen, i.e NIS-LL and Norfolk, the applicant provided comparison between groups on yearly rate of disease progression, based on a regression model from the cross sectional study Fx1A-OS-001 and the data obtained in the Fx-005 study.

Observed Annual Rate of Change in Study Fx-005 (ITT Population) versus the Estimated Annual Mean (SE) Rate of Change in Observational Study Fx1A-OS-001

	Study Fx1A-OS-001	Study Fx-005		
Scale	Untreated ATTR-PN Patients	Tafamidis (N=64)	Placebo (N=61)	P-value (tafamidis versus placebo)
NIS-LL	3.80 (0.43)	1.98 (0.64)	4.14 (0.65)	0.018

Module 2.7.3 (Section 2.1.12.2)

Observed Annual Rate of Change in Study Fx-005 (ITT Population) versus the Estimated Annual Rate of Change in Observational Study Fx1A-OS-001

	Study Fx1A-OS-001	Study Fx-005		
Scale	Untreated ATTR-PN Patients	Tafamidis (N=64)	Placebo (N=61)	P-value (tafamidis versus placebo)
Norfolk QOL-DN	6.6 (0.45)	1.47 (1.19)	5.54 (1.85)	0.121

Module 2.7.3 (Section 2.2.8.6)

Prior to the completion of Study Fx-005, there were no prospectively obtained, longitudinal data on the rate of NIS-LL progression and on the Norfolk QoL progression in untreated ATTR-PN patients. As study Fx-005 included a placebo group followed longitudinally over 18 months, the rate of change in both scores in early ATTR-PN patients could be determined.

The results on annual progression (units/year) based on both scores as observed in study Fx-005 were consistent with the estimated rate of change from Study Fx1A-OS-001, and supported the utility of the NIS-LL and TQOL in documenting disease progression in ATTR-PN even for early stage. Thus, the CHMP considered that comparison of the yearly rate of disease progression between groups validated the clinical relevance of the parameters used.

The CHMP also discussed the choice of the percentage of responder on NIS-LL in terms of the cut-off point for response, i.e. change from baseline<2. A "waterfall" type plot showing differences in response rate across various possible cut-off points (-4 to 10) was presented by the applicant. % of patients responding to treatment using various NIL-LL score threshold definition was provided. Of note, there was no difference between treatments for clinical improvement of NIS-LL with no change or less than 2. However, when considering threshold of 2 and above, the difference in percentage of responders was always in favor of tafamidis. Overall, the definition of NIS-LL response based on change in the score of <2 from baseline was considered acceptable by the CHMP.

In their discussion of the duration of the pivotal study, the CHMP considered that the proposed primary time-point (month 18) for ATTR-PN patients was determined empirically, but was supported by the

regression model determining the yearly rate of disease progression. The CHMP was of the view that the study duration can be accepted as sufficient to show an effect.

In terms of baseline characteristics of patients enrolled in study Fx-005, the CHMP considered that there were numeric differences between the treatment groups with respect to the baseline disease. These differences were observed for NIS-LL and Norfolk QOL at baseline with higher values (corresponding to a more severe disease) in the placebo group compared to the tafamidis group (see Results – Table 13). The CHMP discussed whether these differences may have biased the study results in favour of tafamidis particularly on the analysis of the mean change of NIS-LL from baseline, but considered that as the adjusted analysis provided by the applicant was statistically significant, these differences were no longer of concern.

The CHMP also took into account that 126 out of 128 patients were of stage 1 of the disease (98%) showing that the study population was homogenous. In this context, the CHMP was of the view that no data are available for stages 2 and 3 and requested that this be reflected appropriately in the indication. Thus, the approved the SmPC makes a specific reference to the stage disease in section 4.1 as follows:

"Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment."

Furthermore, the CHMP considered the baseline data of patients who underwent liver transplantation during the study. Of note, transplanted patients presented with more severe disease and longer disease duration than non transplanted patients but were not different between groups. There were no major differences in the delay before transplantation between tafamidis and placebo group. The data on key efficacy endpoints did not seem to show significant differences between transplanted and non-transplanted patients, even though there are limitations to interpreting these data due to the small number of patients per group. Overall, the CHMP was of the view that undergoing liver transplantation tended to be associated with duration of disease rather than with treatment assignment in this study.

Efficacy data and additional analyses

In the primary analyses statistically significant results were not obtained at month 18 (primary time point) for either of the two co-primary endpoints; at month 18, 45% of patients in the tafamidis group had an increase in the NIS-LL of <2 as compared to 29.5% patients in the placebo group (p=0.068). TQOL mean (SD) change from baseline to month 18 was 2.4 (14.6) in the tafamidis group as compared to 6.9 (22.9) in the placebo group (p=0.1157). Of note, a conservative approach (patients who underwent liver transplantation before month 18 were withdrawn from the study and were considered as treatment failures) was applied in the primary analyses.

The CHMP considered that liver transplantation was scheduled before inclusion in the study and patients on the waiting list for whom an organ became available were allowed to be transplanted for ethical reason. Most of study discontinuations were due to liver transplantation and balanced between groups.

A pre-specified sensitivity analysis was conducted by the applicant in order to impute the transplanted patients; this showed statistically significant difference in favour of tafamidis (p=0.0367). However, from the available data, it was unclear why the median baseline NIS-LL was used instead of the individual subject-specific baseline value and how the predicted probability of response was transformed into a binary response. The approach used by the company appeared to be a single imputation method and such methods are known to produce biased estimates of standard errors of treatment effects. A multiple imputation method was considered more reliable by the CHMP. In order

to alleviate these concerns, the CHMP requested two additional analyses where the values for patients who stopped treatment for transplantation would be imputed according to 2 different rules:

1st imputation, where missing data of patients should be imputed on the basis of their last known NIS-LL value and under the assumption of the evolution of their respective group (estimated on the available data, and 2nd imputation: missing data of patients should be imputed on the basis of their last known NIS-LL value and for both groups under the identical assumption of the evolution of the placebo group (estimated on the available data).

The first approach was considered as the most realistic by the CHMP, since the patients would have continued their treatment if no transplant had been available, whereas the second approach was considered as more conservative and more adequate from a regulatory viewpoint.

In either case, the CHMP was of the opinion that the uncertainty of the evolution should be handled by multiple imputation. The imputed dataset was generated by the applicant and both the analysis of responders and of the mean evolution on NIS-LL was performed.

The results of the supplementary analyses are presented in the section Results (tables 19-22).

The analysis with multiple imputation and missing values imputed according to the treatment group can be considered as the "real" ITT analysis and more realistic for handling the missing data. The results provided showed that the NIS-LL responders were not statistically different between groups and confirmed that the mean change from baseline in NIS-LL is different between groups with marginally statistical significance (-2.787, p=0.041); this was supportive of the previous results.

The pre-specified secondary analyses performed in the evaluable population (PP) on the co-primary endpoints (NIS-LL % of responders and TQOL) and on several secondary endpoints, such as the mean NIS-LL change from baseline to visit at month 18, favoured tafamidis to placebo.

As discussed in the Clinical Pharmacology section, results from Fx-005 on the TTR stabilisation are supportive of justifying the 20 mg once daily tafamidis dosing, i.e. adequate TTR stabilisation. The CHMP also considered that this was further supported by TTR stabilisation data obtained in the long-term extension study Fx-006, as the results were consistent with those seen previously. Furthermore, data from study Fx1A-201 indicated that tafamidis is able to stabilize TTR with other mutation than the V30M, as also shown in *in vitro* studies.

The results of the open-label studies in ATTR-PN patients were evaluated by comparing the disease rate of progression of treated patients for both NIS-LL and TQOL between the treatment period of each study and the disease rate progression calculated with the placebo arm of the Fx-005 study. The results of these studies were not considered as robust when compared to the results of controlled studies. The analysis performed did not follow the multiple imputation technique and there were uncertainties regarding data handling. However, when comparing the evolution of NIS-LL in tafamidis treated patients during the 18-month double-blind period and the 12-month open-label period, the rate of change in the NIS-LL score was similar for both periods.

Additional efficacy data needed in the context of a MA under exceptional circumstances

The population enrolled in the pivotal study were patients with V30M mutation at an early stage 1 of the disease; the data on patients with non-V30M ATTR-PN patients originated only from a non-controlled study (Fx1A-201). This study was conducted in 21 patients with non V30M ATTR-PN, which constitutes a population different from the V30M ATTR-PN patients (older patients, more severe

disease, more cardiac impairment). These patients were included at late stage 1 of the disease (mean NIS-LL of 27.6 at inclusion). In this context, the CHMP pointed at limitations of comparisons made between different studies (Fx-005 and Fx1A-201) and different patient populations (V30M versus non V30M mutation). However, as the applicant also provided comparison between the monthly rate of change on the NIS score before vs after treatment with tafamidis and the TTR stabilisation data were favourable irrespective of the mutation, the CHMP considered that extrapolation from V30M to non V30M patients was acceptable.

In their review, the CHMP took into account the fact that due to the rarity of the non V30M patient population a standard double-blind placebo study is not feasible and that the applicant cannot be expected to provide comprehensive evidence. In this context, the CHMP concluded that the MA under exceptional circumstances should be granted subject to a specific obligation to follow non-V30M patients in a proposed sub-study of the THAOS registry. (The THAOS registry is a global, multi-centre, disease registry for the purpose of longitudinal data collection in patients with inherited or wild-type transthyretin amyloidosis and for asymptomatic TTR-variant carriers. The principal aim of the survey is to better understand and characterize the natural history of the disease.)

2.5.4. Conclusions on the clinical efficacy

The dossier is based on a single pivotal phase II/III study. In accordance with the Points to consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99), a submission based on a single pivotal trial can be sufficient provided that the study results are statistically compelling and show clinical relevance.

The results of the single pivotal phase II/III study on the primary analysis on the co-primary criteria (NIS-LL and TQOL) were not met, with statistically significant results not obtained at month 18 for either of the criteria. A sensitivity analysis was conducted in order to impute the transplanted patients and showed statistically significant difference in favour of tafamidis (p=0.0367). Supplementary analyses with different multiple method of imputation provided by the applicant showed that there was no statistical difference between groups regarding NIS-LL percentage of responders. For NIS-LL mean change from baseline, the results with multiple imputations according to the treatment group showed an effect in favour of tafamidis.

The efficacy results are further discussed in the context of the overall benefit-risk balance.

The population enrolled in the pivotal study were patients with V30M mutation at an early stage 1 of the disease; the data on patients with non-V30M ATTR-PN patients originated only from a non-controlled study. The CHMP took into account the orphan status of the product and the fact that due to the rarity of the non V30M patient sub-population a standard double-blind placebo study is not feasible, i.e. the applicant cannot be expected to provide comprehensive evidence. As discussed above, the CHMP concluded that the MA under exceptional circumstances should be granted and considered the following measure necessary to address the missing efficacy data in its context:

Specific obligation:

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

2.6. Clinical safety

Patient exposure

There were 13 clinical studies (controlled and uncontrolled) in the tafamidis development programme and 2 non-interventional observational studies. Tafamidis exposure across the studies included a total of approximately 210 patients-years in 162 patients (over 175 patient-years of exposure in a total of 127 ATTR-PN patients and over 34 patient-years in 35 ATTR-CM patients). The clinical studies supporting the safety evaluation in patients with the target indication (ATTR-PN) were studies Fx-005, Fx-006, Fx1A-201 and Fx1A-303 (interim data). Phase I programme in healthy subjects provided additional evidence for safety evaluation. The exposure is represented by 308 individuals (including 128 healthy subjects) who received at least one dose of tafamidis, 147 ATTR patients for at least 6 months, 113 for at least 12 months and 43 for at least 2 years. Out of 128 V30M patients enrolled in the single pivotal phase II/III study (Fx-005), 22 patients were treated with tafamidis for at least 30 months (these data are included in the dataset of study Fx-006). Patient exposure for the studies supporting safety evaluation in the target population is summarised in table 33.

Table 33

	Patients enrolled (safety population)	Patients exposed (ITT population)	Patients with long term* safety data
Placebo-controlled			
Fx-005	128	125	
Tafamidis group	65	64	59
Placebo group	63	61	58
Open studies			
Fx-006 (extension to Fx-005)	85	85	77
Fx1A-201	21	21	19
Fx1A-303 (interim data)	81(planned n=110)	81	80
Post marketing	NA		
Compassionate use	NA		

** in general this refers to 6 months and 12 months continuous exposure data or intermittent exposure*

In the safety population of Fx-005 (128 patients), mean age was 40 years (+/-12.7) in tafamidis group and 38.1 years (+/-12.8) in the placebo group. Only 5 patients in tafamidis group and 3 in placebo group were >65 years. The planned exposure for this study was 18 months.

In the open-label study Fx-006, a total of 85 patients were included in the safety population: 44 in tafamidis-tafamidis group and 41 in placebo-tafamidis group. The mean age was respectively 41.3 years [26-76] and 39.6 years [24-73]. The percentage of the elderly patients (≥65 years-old) was 13.6% (n=6) and 7.3% (n=3), respectively. The planned exposure during this study was 12 months.

In study Fx1A-201, a total of 21 subjects who had non-V30M transthyretine amyloidosis (mainly elderly) were enrolled and analysed. The planned exposure during this study was 12 months.

Adverse events

Study Fx-005

"Infections and infestations" and "Gastrointestinal disorders" were the SOC with the highest incidence in the tafamidis group (66.2% and 53.8%, respectively); the incidence of infections and infestations was slightly higher in the tafamidis group than in placebo group (66.2% versus 52.4%), while the incidence of gastrointestinal disorders was slightly higher in the placebo group than in the tafamidis group (61.9% versus 53.8%).

Overall, treatment-emergent adverse events (TEAEs) reported more frequently (≥2%) in the tafamidis group compared to placebo included diarrhoea (26.2% versus 17.5%), urinary tract infections (UTI) (23.1% versus 12.7%), pain in extremity (16.9% versus 9.5%), upper abdominal pain (12.3% versus 3.2%), myalgia (7.7% versus 3.2%) and vaginal infections (6.2% versus 1.6%).

A total of 26 (20%) patients (13 patients in each treatment group) discontinued due to liver transplantation. Of the 26 transplanted patients, 8 (30.8%) reported adverse events post-liver transplantation, 5 (38.5%) in the tafamidis group and 3 (23.1%) in the placebo group.

Study Fx-006

"Infections and infestations", "GI disorders", "Nervous system disorders", "Injury, poisoning and procedural complications" and "Eye disorders" were the SOCs reported with the highest incidence in this study.

In the tafamidis-tafamidis group, nasopharyngitis was reported more frequently than in the placebo-tafamidis group (11.4 and 7.3%, respectively). This incidence rate was similar to that observed in the placebo group in study Fx-005 (12.7%).

The greatest difference in TEAE incidence between tafamidis-tafamidis and placebo-tafamidis (and higher in the placebo-tafamidis group) was observed for influenza (6.8 and 17.1%), headache (4.5% and 14.6%), anxiety (2.3 and 12.2%) and urinary tract infections (11.4 and 17.1%, respectively).

Study Fx1A-201
The most commonly reported (≥10%) TEAEs overall were falls (24%), diarrhoea (24%), pain in extremity (19%), dizziness (14%); dyspnoea (14%), vomiting (14%) and constipation (14%). The high proportion of falls (5/21; 24%) and dizziness (3/21; 14%) observed in elderly patients was similar to the one reported in the literature[•], i.e. estimated annual incidence of falls between 22 and 30%. Of note, most patients received antihypertensive drugs as concomitant medication.

Adverse events of special interest

Urinary tract infections (UTI)

In study Fx-005, treatment-emergent UTIs were reported more frequently in tafamidis patients compared to placebo patients, n=15 (23.1%) vs. n=8 (12.7%), respectively. 7 (41%) of 17 tafamidis-treated patients and 5 (50%) of 10 placebo-treated patients had a past medical history of relevant urinary events, such as urinary retention, urinary incontinence and prior UTIs that may have pre-disposed these patients to the UTIs. Of note, in the open label study Fx-006, UTIs occurred more frequently in the first weeks in patients who were switched from placebo to tafamidis. A total of 5 cases of the UTIs were reported in the tafamidis-tafamidis group and 7 in placebo-tafamidis group.

[•] Shumway-Cook- 2009; Stevens 2006

Overall, patients experiencing UTI events in both studies were more frequently women aged around 40 years [23-66]. In both studies, all except for two had autonomic neuropathy symptoms at baseline (predisposing the patient to frequent and recurrent UTI). The majority of events in patients treated with tafamidis were mild to moderate in severity, responsive to antibiotics and not requiring interruption or discontinuation of the study drug. Given the higher incidence of UTI in tafamidis group, a causal relationship between tafamidis and UTIs could not be ruled out. UTI are considered as an important identified risk and reflected in the Risk Management Plan (RMP). No UTI cases were reported in study Fx-1A-201.

Other infections

In study Fx-005, viral infections were reported more frequently in the tafamidis group (46.2%) compared to placebo (42.9%) and were mainly represented by influenza (flu or flu syndrome), nasopharyngitis and upper respiratory tract infections.

One serious case of infection required temporary interruption of tafamidis in study Fx-005. This case of atypical pneumonia was unlikely related to study medication, since no re-occurrence of symptoms was observed upon re-challenge of tafamidis.

In study Fx-005, a higher incidence of vaginal infections in women was observed in tafamidis (18.2%) vs placebo (8.1%); all vaginal infections were mild and non-serious and none required study drug interruption or discontinuation. Although the mechanism of this event is not known, vaginal infection was considered as an important identified risk and included in the RMP.

Diarrhoea

In Fx-005 study, a similar incidence of gastrointestinal motility-type adverse events was reported between the treatment groups; diarrhoea was the only event of this type reported more frequently in tafamidis patients than in placebo patients (n=19 vs 13).

The majority of patients in both treatment groups had pre-existing risk factors of gastro-intestinal motility disorders, autonomic neuropathy or a prior history of diarrhoea. The majority of diarrhoea cases in the tafamidis group was mild to moderate in severity, responsive to symptomatic treatment and did not require interruption or discontinuation of tafamidis treatment. Although diarrhoea is a characteristic symptom of ATTR-PN, given the higher incidence of diarrhoea in the tafamidis group, a causal relationship could not be ruled out. Diarrhoea is considered as an important identified risk and included in the RMP.

No relevant cases of dehydration were reported concomitantly with diarrhoea events in any of the studies.

There were only 2 cases in the tafamidis group in study Fx-005 and one in the placebo-tafamidis group in study Fx-006 requiring antibiotics, suggesting infectious aetiology. Stool cultures were not performed.

Hepatotoxicity

In the pivotal study, two tafamidis-treated patients and one placebo-treated patient had elevation of GGT, ALT and/or AST values to >3x ULN. In study Fx-006, six patients had GGT elevations >3x ULN at least once post-baseline. In each of these patients the elevations of GGT were <5x ULN, were isolated and not associated with elevations of ALT, AST or bilirubin.

In one case, liver function tests began to increase at month 9 with a maximum at month 18. The parameters returned within normal range 36 days after tafamidis discontinuation (end of study) and before enrolment in the open label study. Nonetheless, on day 95 during study Fx-006, the patient experienced again hepatic enzyme increase with ALT of 206 U/l (Normal range: 0-47) without any new course of paracetamol and azithromycin (which were confounding factors for the occurrence of liver function test abnormalities during study Fx-005). Additional information revealed that tests for viral, autoimmune and primary liver disorders (e.g. Wilson´s disease) were negative. The patient continued tafamidis during study Fx-006 and was then enrolled in study Fx1A-303. During this study, ALT and AST remained elevated but were decreasing. Tafamidis was interrupted (with a positive de-challenge), but negative re-challenge was noted after re-introduction of tafamidis three months after. Hepatotoxicity is further addressed in the Discussion section.

Cardiac disorders:

In the pivotal study Fx-005, cardiac disorders were mainly reported in the placebo group 30.2% compared to 15.4% in the tafamidis group. The main AE reported in tafamidis group with a difference from placebo of >2% was bradycardia (3.1% vs 0). Echocardiography parameters were similar in each group of treatment.

Approximately 40% of patients in both treatment groups had an abnormal ECG at baseline, with the most common abnormalities being abnormal conduction (approximately 30% per group): first degree AV block and left anterior hemiblock.

On-treatment, the most frequent post-baseline (overall at any time) abnormalities reported were abnormal rhythm (12.3% tafamidis vs. 6.3% placebo), arrhythmia (approximately 9% in both groups) and abnormal conduction (not specified) (3.1% tafamidis vs. 11.1% placebo). The most commonly reported treatment-emergent rhythm abnormalities included sinus tachycardia and atrial fibrillation.

Of note, 4 (6.2%) tafamidis-treated patients and 1 (1.6%) placebo-treated patient had a QTc-F >500 ms during the study. In addition, one (1.6%) placebo-treated patient (but no tafamidis-treated patients) had a change in QTc-F >60 ms during the study.

Orthostatic hypotension

Analysis of changes of vital signs indicative of possible orthostatic hypotension was performed, because of the high prevalence of cardiovascular autonomic dysfunction and potential for adverse clinical manifestations in ATTR-PN patients. In study Fx-005, a slight increase of vital signs related to possible orthostatic hypotension was observed at weeks 2 and 4, in the tafamidis group compared to placebo (35.9% at 2 weeks and 34.4% at 4 weeks in the tafamidis group versus 25.4% at 2 weeks and 25.8% at 4 weeks in placebo); this trend was reversed after 8 weeks. The percentage of orthostatic hypotension increased in both groups compared with baseline, from less than 30% at baseline in both groups compared to 65-70% on treatment. In study Fx-006, the incidence was similar between tafamidis-tafamidis and placebo-tafamidis groups.

According to the data provided, there is no evidence that treatment by tafamidis in study Fx-005 is associated with a higher incidence of orthostatic hypotension and there are no data suggesting an increase of this type of events with longer exposure (lower percentage of patients with at least one adverse event of interest in study Fx-006).

Serious adverse event/deaths/other significant events

No serious adverse events or deaths were reported in the healthy or in the hepatically impaired subjects during the Phase I clinical studies.

A summary of the incidence of treatment-emergent serious adverse events in the ATTR-PN patients, sorted by descending incidence in the tafamidis group, is presented in table 34:

Table 34

			Open Label Studies				
	Fx-005		Fx-006		Fx1A-201	Total	Overall
MedDRA Preferred Term	Tafamidis (N=65) n (%)	Placebo (N=63) n (%)	T-T (N=44) n (%)	P-T (N=41) n (%)	Tafamidis (N=21) n (%)	Tafamidis (N=106) n (%)	Tafamidis (N=127) n (%)
Patients With At Least 1 Event	6 (9.2)	5 (7.9)	4 (9.1)	4 (9.8)	8 (38.1)	16 (15.1)	22 (17.3)
Urinary tract infection	2 (3.1)	0	0	1 (2.4)	0	1 (0.9)	3 (2.4)
Vomiting	0	1 (1.6)	1 (2.3)	1 (2.4)	0	2 (1.9)	2 (1.6)
Fall	0	0	0	0	2 (9.5)	2 (1.9)	2 (1.6)
Anaemia	0	1 (1.6)	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Atrioventricular block	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Conduction disorder	1 (1.5)	0	0	0	0	0	1 (0.8)
Coronary artery stenosis	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Faecaloma	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Nausea	0	1 (1.6)	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Subileus	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Malaise	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Hypersensitivity	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8)
Catheter sepsis	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8)
Infection	0	0	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Localised infection	1 (1.5)	0	0	0	0	0	1 (0.8)
Meningitis	0	0	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Osteomyelitis	0	0	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Pneumonia	1 (1.5)	0	0	0	0	0	1 (0.8)
Viral infection	1 (1.5)	0	0	0	0	0	1 (0.8)
Ankle fracture	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Avulsion fracture	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Blood electrolytes decreased	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8)
Dehydration	0	0	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Arthritis	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Lymphoma	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8)
Transient ischaemic attack	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Urinary retention	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Skin lesion	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8)
Urticaria	1 (1.5)	0	0	0	0	0	1 (0.8)
Carpal tunnel decompression	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Cardiac amyloidosis	0	1 (1.6)	0	0	0	0	0
Catheter site phlebitis	0	1 (1.6)	0	0	0	0	0
Oedema peripheral	0	1 (1.6)	0	0	0	0	0
Cellulitis	0	1 (1.6)	0	0	0	0	0
Lymphangitis	0	1 (1.6)	0	0	0	0	0
Staphylococcal infection	0	1 (1.6)	0	0	0	0	0
Burns third degree	0	1 (1.6)	0	0	0	0	0
Syncope	0	1 (1.6)	0	0	0	0	0
Pneumothorax	0	1 (1.6)	0	0	0	0	0
Skin ulcer	0	1 (1.6)	0	0	0	0	0
Hypertensive emergency	0	1 (1.6)	0	0	0	0	0

Note: T-T reflects tafamidis treatment in both Study Fx-005 and Fx-006. P-T reflects placebo treatment in Study Fx-005 and tafamidis treatment in Study Fx-006.

Overall, 22 of 127 (17.3%) tafamidis treated patients experienced at least one serious adverse event. The incidence of SAEs was significantly higher in study Fx1A-201 (38.1%) than in Studies Fx-005 (9.2%) and Fx-006 (9.1% for the tafamidis-tafamidis group and 9.8% for the placebo-tafamidis group). The higher incidence in Study Fx1A-201 was possibly due to the underlying differences in the characteristics of the patient population enrolled, with patients in this study being on average 20 years older than patients in Study Fx-005 and with more co-morbidities reported in medical histories.

Urinary tract infection, vomiting and falls were the only SAEs reported in more than one patient treated with tafamidis. Each of the serious cases of urinary tract infection occurred in patients with pre-existing risk factors for infection.

The SAEs of infection included localized infection, pneumonia and viral infection in study Fx-005 patients and catheter sepsis, meningitis, osteomyelitis and infection in study Fx-006. In each of these cases, the infection resolved following appropriate antibiotic treatment. One case of meningitis had an atypical presentation and was ultimately presumed secondary to TB.

The analysis of SAEs by gender revealed similar findings to the overall analysis; there were too few patients older than age 65 to make any meaningful interpretation of the analysis by age. No trend of increasing incidence of SAEs over time (i.e., from the first 6 months of treatment to the later 6-month periods) was observed, at no time was the 6-month incidence rate of SAEs higher than 7.1%.

Treatment-emergent adverse events judged by the investigator to be at least possibly related to study treatment, sorted by descending incidence in the tafamidis group, are summarised in table 35.

Table 35

			Open Label Studies				Overall
	Fx-005		Fx-006		Fx1A-201	Total	
MedDRA Preferred Term	Tafamidis (N=65) n (%)	Placebo (N=63) n (%)	T-T (N=44) n (%)	P-T (N=41) n (%)	Tafamidis (N=21) n (%)	Tafamidis (N=106) n (%)	Tafamidis (N=127) n (%)
Patients With At Least One SAE At Least Possibly Related to Study Treatment	2 (3.1)	2 (3.2)	1 (2.3)	1 (2.4)	3 (14.3)	5 (4.7)	7 (5.5)
Ankle fracture	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Lymphoma	0	0	1 (2.3)	0	0	1 (0.9)	1 (0.8%)
Malaise	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Meningitis	0	0	0	1 (2.4)	0	1 (0.9)	1 (0.8)
Transient ischaemic attack	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Urinary retention	0	0	0	0	1 (4.8)	1 (0.9)	1 (0.8)
Urinary tract infection	1 (1.5)	0	0	0	0	0	1 (0.8)
Urticaria	1 (1.5)	0	0	0	0	0	1 (0.8)
Anaemia	0	1 (1.6)	0	0	0	0	0
Syncope	0	1 (1.6)	0	0	0	0	0
Vomiting	0	1 (1.6)	0	0	0	0	0

Note: T-T reflects tafamidis treatment in both Study Fx-005 and Fx-006. P-T reflects placebo treatment in Study Fx-005 and tafamidis treatment in Study Fx-006.

Overall, 7 of 127 (5.5%) tafamidis treated patients experienced at least one serious adverse event judged by the investigator to be at least possibly related to study treatment. The incidence of at least possibly related SAEs was higher in study Fx1A-201 than in studies Fx-005 and Fx-006, possibly due to the underlying differences in the characteristics of the patient population enrolled, as described above. No type of SAE judged to be at least possibly related to study medication was reported in more than one patient.

There were seven deaths in the ATTR-PN patients, five in the pivotal study Fx-005; these cases occurred only post liver transplantation: three deaths occurred in patients who were on placebo prior to liver transplantation and 2 deaths occurred in the tafamidis group. Each of these two deaths was attributed to treatment associated with liver transplant, one patient died shortly after liver transplantation due to an unknown cause, while the other died due to cardiac tamponade as a complication of pacemaker insertion post liver transplantation. Of note, patients undergoing liver transplantation were discontinued from the study medication prior to the transplantation and thus, the deaths occurred only after patients had already been discontinued from tafamidis. The five cases of death are summarised in table 36:

Table 36

Study Number	Treatment		Age (yrs)	Sex	Duration of exposure (Days)	Diagnosis	Cause of Death	Location of narrative description
Fx-005	Tafamidis		54	Female	328	ATTR-PN	Cardiac tamponade after cardiac manipulation for temporary artificial pacemaker post liver transplantation	Section 14.3.3, Clinical Study Report Fx-005
	Tafamidis		37	Female	560	ATTR-PN	Death after liver transplantation, unknown cause	
	Placebo		41	Female	457	ATTR-PN	Hepatic failure after transplant	
	Placebo		63	Female	437	ATTR-PN	Sepsis post liver transplant	
	Placebo		35	Female	336	ATTR-PN	Death after liver transplantation, unknown cause	

In the ongoing study Fx1A-303, a total of fourteen SAEs have been reported in eight patients (cut-off date: 9 December 2010). Most of them were attributed to the underlying conditions particularly nervous system, gastrointestinal and cardiac disorders. The two deaths occurring during Fx1A-303 study were reported in patients with ATTR-PN on tafamidis and were not associated with liver transplantation. These patients were older than the patients who died after liver transplantation and with stage 3 disease at the time of tafamidis initiation. These deaths seemed related to progression of the underlying disease.

Laboratory findings

There were no meaningful differences in mean laboratory parameters between the placebo and tafamidis treatment groups in study Fx-005. The overall tafamidis-treated population demonstrated similar trends for the laboratory parameters to those observed in the pivotal study Fx-005.

The incidence of treatment-emergent potentially clinically significant (PCS) laboratory values was generally similar between the treatment groups in study Fx-005, with no apparent increase in PCS values in tafamidis-treated patients. Overall, changes in liver function tests were unremarkable, except for one patient who had increase in liver function tests three times above the upper limit of normal associated with tafamidis treatment during participation in Studies Fx-005 and Fx-006. However, no constitutional signs or symptoms were reported and no increase in bilirubin was noted in this patient.

Average changes over time in vital sign parameters were minor and not clinically relevant; no trends were observed and outcomes were similar between treatment groups and across studies. Changes in both heart rate and QTcF (as well as the other ECG parameters) over time were similar and not clinically meaningful between the placebo and tafamidis patients in study Fx-005; the overall tafamidis treatment group demonstrated similar trends over time, indicating that treatment with tafamidis up to 30 months does not meaningfully affect ECG parameters. Tafamidis treatment at doses up to three times the dose to be marketed did not impact cardiac repolarization in healthy volunteers, nor did tafamidis cause significant dysrhythmias in ATTR-PN patients.

Transthyretin (pre-albumin) is a transport protein for retinol binding protein-vitamin A complex and thyroxin. As tafamidis binds to the thyroxine binding site of TTR, a careful assessment of the impact of tafamidis on TTR, RBP and thyroid hormone levels was performed. In Fx-005, mean increases from baseline in TTR (increases ranging from 4 to 6 mg/dl) were observed at every post-baseline study visit for tafamidis-treated patients, with the maximum increase observed at the 8 week visit and no further

increase was observed at later time points. Similarly to TTR, mean increases in RBP levels (range 2 to 11 mg/dl) were observed in tafamidis patients. In Fx-006, TTR and RBP values in the tafamidis-tafamidis group were constant over time.

With respect to thyroid function no significant changes were observed from baseline; the mean change was similar to placebo treated patients at all time points in the pivotal study Fx-005. The mean and median T4, free T4 and TSH values were within the normal ranges at baseline and at all time points during Fx-006 study (see Discussion).

Safety in special populations

Pregnancy

Pregnant and lactating women were excluded from the clinical trial protocols. Nevertheless, in Fx-005, one pregnancy occurred in a tafamidis-treated patient (healthy baby) and one in a placebo-treated patient. No other pregnancies were reported during other studies.

Paediatric population

There was no data in the use of tafamidis in children and adolescents less than 18 years old (the youngest patient in the tafamidis population was 24 years old).

Elderly population

Overall, data on the elderly population were scarce since only 8 patients >65 years old were enrolled in study Fx-005 (5 patients in tafamidis group and 3 in placebo group).

Renal impairment population

Data on patients with renal impairment are very scarce since only two patients with CrCl <50ml/min and 10 with CrCl between 50 and 80 ml/min were enrolled in pivotal study.

Immunological events

In study Fx-005 study, only one TEAE (hypersensitivity) was reported in the SOC "Immune system disorders" (placebo group). No signal emerged from these data regarding the immunological events.

In study Fx-006, one serious case of hypersensitivity was reported in the tafamidis-tafamidis group. Due to previous treatment with cotrimoxazole (known to trigger allergic reactions) and negative re-challenge, the role of tafamidis was considered doubtful.

Safety related to drug-drug interactions and other interactions

Tafamidis was highly bound to plasma proteins (>99%) across all species tested and decreased the human plasma protein binding of prednisone by approximately 10%, with no impact on the protein binding of tacrolimus, cyclosporine or warfarin; this indicated no clinical effect during co-administration with other highly protein-bound drugs.

Discontinuation due to adverse events

In study Fx-005, a total of seven (5.5%) patients discontinued due to a treatment-emergent adverse event, four (6.2%) tafamidis-treated patients and three (4.8%) placebo-treated patients. Adverse events leading to discontinuation for the tafamidis-treated patients included diarrhoea, nausea, pregnancy and urticaria. AEs leading to discontinuation for placebo-treated patients included cardiac amyloidosis, nausea, fatigue and paresthesia (both in one patient). No patients discontinued study Fx-006 due to adverse events.

In Fx1A-201, one 74-year-old female patient with a history of bradycardia, orthostasis, hypertension and ATTR-related congestive heart failure discontinued due to mild transient ischemic attack (occurring 31 days after tafamidis initiation).

In Fx1A-303, except for the two deaths referred to above, no subject was withdrawn from the study due to an adverse event (cut-off date: 9 December 2010).

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Given the prevalence of the condition, the overall safety database was considered reasonable. The safety evaluation of tafamidis in the target population, i.e. patients suffering from ATTR-PN, was based on clinical studies Fx-005 (pivotal study), Fx-006 and Fx-1A201, data from phase I clinical programme in healthy subjects and interim data from study Fx1A-303. Study Fx1B-201 in a subset of ATTR patients with cardiomyopathy (ATTR-CM) generated supportive safety data.

Overall, no major safety concerns were identified in the target population treated with tafamidis. The adverse events were generally mild to moderate in severity, mostly represented by urinary tract infection, infections (mainly respiratory infections), diarrhoea, headache, pain in the extremity and vomiting. In particular, urinary tract infections, diarrhoea, upper abdominal pain and vaginal infection were considered as important identified risks by the CHMP and thus, they were included in the Risk Management Plan and reflected in section 4.8 of the SmPC as follows:

"Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10):

Infections and infestations
Very common: Urinary tract infection
Common: Vaginal infection

Gastrointestinal disorders
Very common: Diarrhoea
Common: Upper abdominal pain"

Based on a significant case of liver function test abnormalities, hepatotoxicity was considered as an important potential risk, even though a negative re-challenge was finally seen in study Fx1A-303 for the affected patient. Several possible mechanisms for the potential hepatotoxicity were outlined by the applicant, such as enzyme induction, metabolism or thyroid hormone disruption. The CHMP considered that only 65 patients were exposed to tafamidis in the pivotal study and therefore, identification of one case of hepatotoxicity might be of clinical relevance. In this context, the CHMP concluded that hepatotoxicity will be further monitored in the post-authorisation setting by means of routine pharmacovigilance activities including use of data capture aid for hepatotoxicity, collection of data in

the ongoing study Fx1A-303 and collection of data on adverse events in the TTR-associated amyloidosis outcomes survey (THAOS). The CHMP considered that the data from the THAOS survey will be provided on an annual basis, i.e. synchronized with the timing of the annual re-assessment. These pharmacovigilance measures were deemed satisfactory by the CHMP to further characterize this potential risk.

As described in the non-clinical section, the effect on the thyroid function was also discussed in detail by the CHMP. In the pivotal study Fx-005 no significant changes for thyroid functions were seen from baseline and mean change was similar to placebo treated patients at all time points. The values of thyroid function parameters were also within the normal ranges at baseline and at all time points during study Fx-006. Based on these observations the CHMP considered that the theoretical risk of tafamidis on thyroid function was unlikely, but could not be completely ruled out. In particular, the CHMP was of the opinion that despite absence of relevant effect on the thyroid function, tafamidis treatment may have subtle impact on the thyroid function due to the competition to the binding proteins. In this context, the CHMP was of the opinion, that changes of thyroid function should be considered as an important potential risk in the RMP.

Conduction and rhythm disorders were thoroughly analyzed by the applicant. Based on the data provided, no increased risk of conduction or rhythm abnormalities associated with the use of tafamidis was identified in the studies.

Based on the data provided, the CHMP considered that there is no evidence that treatment by tafamidis in study Fx-005 was associated with a higher incidence of orthostatic hypotension or that the data suggest an increase of this type of events with longer exposure.

The CHMP considered that data on special populations, such as the elderly and patients with renal impairment are scarce, but considered this in the context of the rare nature of the disorder as acceptable. Only one pregnancy in a patient treated with tafamidis was reported. The mother gave birth to a healthy baby without any congenital abnormality. Due to the limited data on pregnancy, no conclusions on the use of tafamidis could be made and the use of the product during pregnancy was not recommended.

Additional safety data needed in the context of a MA under exceptional circumstances

The population enrolled in the pivotal study were patients with V30M mutation at an early stage 1 of the disease; the data on patients with non-V30M ATTR-PN patients originated only from a non-controlled study (Fx1A-201). This study was conducted in 21 patients with non V30M ATTR-PN, which constitutes a population different from the V30M ATTR-PN patients (older patients, more severe disease, more cardiac impairment). The CHMP considered that as part of the sub-study Fx-R-001-S2 requested as a specific obligation, safety data in the non-V30M ATTR-PN patients will be collected, which should contribute to further characterising the safety profile in this particular sub-population of patients.

2.6.2. Conclusions on the clinical safety

The safety of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The safety conclusions are further discussed in the context of the overall benefit-risk balance.

The CHMP concluded that the MA under exceptional circumstances should be granted and considered the following measure necessary to address the missing safety data in its context:

Specific obligation:

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

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 37 Summary of the EU-RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Urinary tract infection	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Urinary tract infection is included in SmPC Section 4.8 'Undesirable Effects' (Infections and infestations: Very common: Urinary tract infection) and in the PIL.
Diarrhoea	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Diarrhoea is included in SmPC Section 4.8 'Undesirable Effects' (Gastrointestinal disorders: Very common: Diarrhoea) and in the PIL.

Upper abdominal pain	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Upper abdominal pain is included in SmPC Section 4.8 'Undesirable Effects' (Gastrointestinal disorders: Common: Upper abdominal pain), and stomachache and abdominal pain included in the PIL.
Vaginal infection	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Vaginal infection is included in SmPC Section 4.8 'Undesirable Effects' (Infections and infestations: Common: Vaginal infection) and in the PIL.
Important potential risks		
Hepatotoxicity	Routine pharmacovigilance including use of data capture aid Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: SmPC Section 4.2 'Hepatic and renal impairment: No dosage adjustment is required for patients with renal or mild and moderate hepatic impairment. Vyndaqel has not been studied in patients with severe hepatic impairment and caution is recommended (see section 5.2)'.
Hypersensitivity reactions	Routine pharmacovigilance including use of data capture aid (to be developed) Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Hypersensitivity to the active substance or to any of the excipients is included in SmPC Section 4.3 'Contraindications' and in the PIL.

Reproductive toxicity	Routine pharmacovigilance including collection of intrauterine exposure data. Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO). Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Inclusion of "Women of childbearing potential should use appropriate contraception when taking Vyndaqel (see section 4.6)" in SmPC Section 4.4 'Special Warnings and Precautions for Use', "Women of childbearing potential: Contraceptive measures should be used by women of childbearing potential during treatment with Vyndaqel, and for one month after stopping treatment, due to the prolonged half life, and "Pregnancy There are no data on the use of Vyndaqel in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Vyndaqel is not recommended during pregnancy and in women of childbearing potential not using contraception." in SmPC Section 4.6 'Fertility, pregnancy, and lactation', and corresponding information in the PIL. Additional: Physician Information Leaflet with important details on THAOS registry and TESPO programme.
Changes in Thyroid Function, particularly in pregnant women	Routine pharmacovigilance including collection of intrauterine exposure data Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO). Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	Routine: Inclusion of "Women of childbearing potential should use appropriate contraception when taking Vyndaqel (see section 4.6)" in SmPC Section 4.4 'Special Warnings and Precautions for Use', "Women of childbearing potential: Contraceptive measures should be used by women of childbearing potential during treatment with Vyndaqel, and for one month after stopping treatment, due to the prolonged half life", and "Pregnancy: There are no data on the use of Vyndaqel in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Vyndaqel is not recommended during pregnancy and in women of childbearing potential not using contraception." in SmPC Section 4.6 'Fertility, pregnancy, and lactation', and corresponding information in the PIL.
Important missing data		
Safety and efficacy in elderly patients	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	In SmPC Section 4.2 'Posology and method of administration': "*Elderly:* No dosage adjustment is required for elderly patients (≥ 65 years)".

Longer term safety	Routine pharmacovigilance Continue data collection in ongoing Study Fx1A-303 'Open-Label Safety and Efficacy Evaluation of Fx-1006A in Patients with Transthyretin Amyloidosis'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS registry) Collect data from Study Fx-R-001-S2 'A THAOS Sub-study Evaluating the Effects of Tafamidis on Disease Progression in Patients with Non-V30M Mutations and Symptomatic Neuropathy'. Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS), amended protocol Fx-R-001.	In SmPC Section 5.1 'Pharmocodynamic properties': "In the open-label extension study the rate of change in the NIS-LL during the 12 months of open label treatment was similar to that observed in the previous 18 months. Although data are limited (one open label study in 21 patients), taking into account the mechanism of action of Vyndaqel and the results on TTR stabilisation, Vyndaqel may be beneficial in patients with stage 1 TTR amyloid polyneuropathy due to mutations other than V30M." Additional: Physician Information Leaflet with important details on THAOS registry and TESPO programme.

The CHMP, having considered the data submitted, was of the opinion that the pharmacovigilance activities in addition to the use of routine pharmacovigilance, as summarised in the EU-RMP Summary table (table 37), are needed to investigate further some of the safety concerns.

The CHMP, having considered the data submitted, was of the opinion that the following additional risk minimisation activity was required: a Physician Information Leaflet with important details on the THAOS registry and TESPO programme, as referenced in the EU-RMP Summary table (table 37).

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

1. The assessment of the synopsis for the amended protocol (THOAS Study Fx-R-001): In the objective to collect adverse drug reaction data in patients with TTR amyloidosis treated with tafamidis the safety concerns urinary tract infection, diarrhoea, upper abdominal pain, vaginal infection, safety and efficacy in elderly patients and long term safety are missing. The synopsis should reflect the safety concerns to monitor in line with EU-RMP table 25. Furthermore, the RMP does not mention if the potential risk of thyroid function changes will be addressed by this study. The synopsis should be updated accordingly and the final protocol submitted within three months post Opinion.
2. In EU-RMP section 2.2.1.6 the reference to the specific obligation should be deleted.
3. In EU-RMP table 26 for the potential risk of changes to thyroid function Study Fx1A-303 is not mentioned in the action plan but the annual safety report is included as a milestone. The applicant should clarify if Study Fx1A-303 will address this safety concern. In the same context the applicant should clarify if the amended protocol Fx-R-001 will address the potential risk of changes of thyroid function. EU-RMP table 25 should be aligned accordingly.
4. In EU-RMP table 26 it is not clear why Study Fx1A-303 was removed from titles of protocols row.
5. The physician leaflet intended to highlight to HCP the existence of THAOS registry and TESPO programme should be linked to relevant safety concerns (i.e. potential risk of reproductive toxicity and important missing information on long term safety) in table 27, rather than to each identified risk.
6. The applicant should update EU-RMP table 27 with the status for amended study protocol Fx-R-001 (THAOS registry) and protocol synopsis Fx-R-001-S2 (THAOS sub-study) and provide in EU-RMP section '2.6. Summary of outstanding actions, including milestones' a tabulated overview of outstanding actions of the pharmacovigilance plan including milestones. The final protocol of Fx-R-001-S2 sub-study should be submitted within three months post opinion.
7. The applicant should update EU-RMP table 29 in line with all the above changes.

2.8. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The mode of action of tafamidis was supported by results of the clinical pharmacology and clinical efficacy studies (pivotal study) and is linked to the physiopathology of the disease, i.e. TTR dissociation followed by accumulation of monomers and deposition of amyloid in several tissues. As discussed in the Clinical Pharmacology section, results from Fx-005 on the TTR stabilisation were supportive of justifying the 20 mg once daily tafamidis dosing, i.e. adequate TTR stabilisation. The CHMP also considered that this was further supported by TTR stabilisation data obtained in the long-term extension study Fx-006, as the results were consistent with those seen previously. This TTR stabilisation effect of tafamidis was observed on the wild-type TTR as well as on several TTR mutations including the V30M and non-V30M mutations. In particular, data from study Fx1A-201 indicated that tafamidis was able to stabilize TTR with other mutation than the V30M, as also shown in *in vitro* studies.

As described in the Clinical efficacy section, the pre-specified secondary analyses performed in the evaluable population (PP) on the co-primary endpoints (NIS-LL % of responders and TQoL) and on several secondary endpoints, such as the mean NIS-LL change from baseline to visit at month 18, favoured tafamidis to placebo. In a supplementary multiple imputation analysis, the mean change from baseline in NIS-LL was statistically different between the treatment groups, supporting the previous results. The CHMP considered that the observed effects were clinically relevant.

Of note, tafamidis is the first oral pharmacological treatment proposed in this indication for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment; currently, the only available treatment alternative is the orthotopic liver transplantion.

Uncertainty in the knowledge about the beneficial effects

One pivotal study was conducted in 125 ATTR-PN patients with V30M mutation. The primary objective of this study was to evaluate the effect of tafamidis 20 mg once daily on disease progression over 18 months using two co-primary criteria, i.e. responders on NIS-LL score, defined as patients with a NIS-LL score change from baseline <2 points at month 18, and change from baseline of the TQOL score (Total Norfolk quality of life score).

Applying a conservative approach (patients who underwent liver transplantation before month 18 were withdrawn from the study and were considered as treatment failures), statistically significant results were not obtained at month 18 (primary time point) for either of the two co-primary endpoints; at month 18, 45% of patients in the tafamidis group had an increase in the NIS-LL of <2 as compared to 29.5% patients in the placebo group (p=0.068). TQOL mean (SD) change from baseline to month 18 was 2.4 (14.6) in the tafamidis group as compared to 6.9 (22.9) in the placebo group (p=0.1157).

In this context, the CHMP considered that liver transplantation was scheduled before inclusion in the study and patients on the waiting list for whom an organ became available were allowed to be transplanted for ethical reason. Most of study discontinuations were due to liver transplantation and balanced between groups. When the evaluable population is taken into account, the responder on NIS-LL scores were statistically different between tafamidis and placebo at month 18. A statistically significant difference in favour of the tafamidis group at month 18 was also observed for TQOL.

The description of the transplanted population showed that transplanted patients presented with a more severe disease and longer disease duration than non transplanted patients, but were not differently represented in the two groups. In addition, there were no major differences in the interval to transplantation between tafamidis and placebo group. The efficacy data did not seem to show significant differences between transplanted and non transplanted patients, but the interpretation of these data was considered difficult due to the low number of patients per group. Nevertheless, the CHMP was of the view that transplantation does not seem to be related to the treatment group.

A sensitivity analysis was conducted to impute patients who underwent liver transplantation. The approach used by the applicant was confirmed by supplementary analyses with other imputation methods and was considered supportive, as statistically significant difference for mean NIS-LL change from baseline, favouring tafamidis, was shown.

The CHMP considered that the familial amyloid polyneuropathy is a length-dependent condition with a pre-dominant progressive sensory loss. On the NIS-LL score, the maximum total score possible for the sensory component is 16/88 points compared to the maximum total score possible for the motor component of 64/88. Since the condition manifests predominantly as a sensory neuropathy, the ability of NIS-LL to properly evaluate disease progression in ATTR-PN was considered by the CHMP. In order to provide more data on the clinical relevance of the criteria chosen, i.e NIS-LL and Norfolk, the applicant provided comparison between groups on yearly rate of disease progression, based on a regression model from the cross sectional observational study Fx1A-OS-001 and the data obtained in the Fx-005 study.

The results on annual progression based on both scores as observed in study Fx-005 were consistent with the estimated rate of change from Study Fx1A-OS-001 and supported the utility of the NIS-LL and TQOL in documenting disease progression in ATTR-PN. Thus, the CHMP considered the effects observed on the co-primary parameters clinically relevant.

The CHMP discussed the duration of the pivotal study and the proposed primary time-point (month 18), which was determined empirically. In this context, the CHMP considered that the regression model used to determine the yearly rate of disease progression was valid and was of the view that the study duration can be accepted as sufficient to show an effect in the ATTR-PN patients.

The CHMP also took into consideration results of the open-label studies in ATTR-PN V30M; patients were evaluated by comparing the disease rate of progression in tafamidis treated patients for both NIS-LL and TQOL between the treatment period of each study and the disease rate progression calculated with the placebo arm of the Fx-005 study. These results suggested stability of the disease and maintenance of effect. Nevertheless, the CHMP considered that results of open studies are not as robust as results of controlled studies, that the analyses performed did not follow the multiple imputation technique and that there were uncertainties regarding data handling. However, when comparing the evolution of NIS-LL in tafamidis treated patients during the 18-month double-blind period and the 12-month open-label period, the rate of change in the NIS-LL score was similar for both periods.

The population enrolled in the pivotal study were patients with V30M mutation at an early stage 1 of the disease; the data on patients with non-V30M ATTR-PN patients originated only from a non-

controlled study (Fx1A-201). This study was conducted in 21 patients with non V30M ATTR-PN, which constitutes a population different from the V30M ATTR-PN patients (older patients, more severe disease, more cardiac impairment). These patients were included at late stage 1 of the disease (mean NIS-LL of 27.6 at inclusion). In this context, the CHMP pointed at limitations of comparisons made between different studies (Fx-005 and Fx1A-201) and different patient populations (V30M versus non V30M mutation). However, as the applicant also provided comparison between the monthly rate of change on the NIS score before vs after treatment with tafamidis and the TTR stabilisation data were favourable irrespective of the mutation, the CHMP considered that extrapolation from V30M to non V30M patients was acceptable. The SmPC section 5.1 is phrased accordingly, i.e. addressing the expected beneficial effect in patients with mutations other than V30M.

Risks

Unfavourable effects

Overall, no major safety concerns were identified in the target population treated with tafamidis. The adverse events were generally mild to moderate in severity, mostly represented by urinary tract infection, infections (mainly respiratory infections), diarrhoea, upper abdominal pain, headache, pain in the extremity and vomiting.

Infections (mainly represented by the urinary tract infections) and infestations were the main events reported in the tafamidis group in the pivotal study Fx-005. In this study, the UTIs were observed in 23.1% of patients in tafamidis group versus 12.7% in placebo group. The majority of events was responsive to antibiotics and did not require interruption or discontinuation of the study drug. Given the higher incidence of UTIs in the tafamidis group, a causal relationship between tafamidis and UTI could not be ruled out and the UTIs were considered as an important identified risk by the CHMP.

A higher incidence of vaginal infections in women was observed in tafamidis (18.2%) vs placebo (8.1%) in the pivotal study; all vaginal infections were mild and non-serious and none required study drug interruption or discontinuation. Although the mechanism of this event is not known, vaginal infection is considered as an important identified risk.

Diarrhoea was reported more frequently in patients treated with tafamidis. Among the two cases of diarrhoea which were considered severe, one led to drug discontinuation due to worsening of diarrhoea. The role of tafamidis in this case remained unclear. Despite diarrhoea being typical of ATTR-PN, given the higher incidence of diarrhoea in the tafamidis group, the CHMP concluded that a causal relationship could not be ruled out and diarrhoea was considered as an identified risk.

Conduction and rhythm disorders were thoroughly analyzed by the applicant. Based on the data provided, no increased risk of conduction or rhythm abnormalities associated with the use of tafamidis was identified in the studies.

Uncertainty in the knowledge about the unfavourable effects

Based on one case of liver function test abnormalities, hepatoxicity was considered as an important potential risk. Several possible mechanisms (enzyme induction, metabolism and thyroid hormone disruption) were proposed as underlying the potential hepatotoxicity, but the relationship remains uncertain. Although a negative re-challenge was eventually observed in study Fx1A-303 in the affected patient, this unfavourable effect was taken into account in the context of a limited exposure to tafamidis in the pivotal study (65 patients).

The CHMP considered that data on special populations, such as the elderly and patients with renal impairment are scarce, but considered this in the context of the rare nature of the disorder as acceptable. Only one pregnancy in a patient treated with tafamidis was reported, with no congenital abnormality in the newborn. Due to the limited data on pregnancy, no conclusions on the use of tafamidis could be made and the use of the product during pregnancy was not recommended.

The effect on the thyroid function was also discussed in detail by the CHMP. In the pivotal study Fx-005 no significant changes for thyroid functions were seen from baseline and mean change was similar to placebo treated patients at all time points. The values of thyroid function parameters were also within the normal ranges at baseline and at all time points during study Fx-006. Based on these observations the CHMP considered that the theoretical risk of tafamidis on thyroid function was unlikely, but could not be completely ruled out. In particular, the CHMP was of the opinion that despite absence of relevant effect on the thyroid function, tafamidis treatment may have subtle impact on the thyroid function due to the competition to the binding proteins. In this context, the CHMP was of the opinion, that changes of thyroid function should be considered as an important potential risk in the RMP.

The CHMP noted that in the chromosomal aberration assay in human peripheral lymphocytes, a dose-dependant increase of polyploidy was observed in the presence of S9. Considering the unclear relevance of the finding and the large safety margins regarding micronucleus induction (>70) as well as the safety margin regarding polyploidy in the chromosome aberration assay (=18), the CHMP concluded that in the context of a serious disease with a lack of therapeutic options, this finding did not impact negatively on the benefit-risk balance of tafamidis. One impurity with an unclear genotoxic potential was seen in the study on impurities. Due its negligible levels in the final product, the CHMP was of the opinion that this finding would not impact on the benefit-risk balance, either.

Benefit-risk balance

Importance of favourable and unfavourable effects

Tafamidis is the first oral pharmacological treatment proposed in the treatment of ATTR-PN patients, which is a severe, progressive orphan disease, with a fatal evolution in around 10 years. The mode of action of tafamidis is linked to the pathophysiology of the disease, with a TTR stabilisation effect on several TTR mutations and wild-type TTR. One pivotal double blind placebo controlled study has been conducted in 128 ATTR-PN patients with V30M mutation. This study failed to attain its primary objectives. However, the other pre-specified analyses and results on secondary criteria showed statistically significant differences in favour of tafamidis. Analyses with multiple imputations showed a statistically significant difference in mean change from baseline for the NIS-LL score. The effects observed were considered clinically relevant. Supplementary analyses performed by the applicant, determining the yearly rate of progression of the disease and analyses of efficacy according to different thresholds for responders also allowed to validate the clinical relevance of the effect.

Tafamidis was well tolerated across studies in both healthy volunteers and patients with ATTR-PN. Overall, no major safety concerns were identified in the target population treated with tafamidis. The adverse events were generally mild to moderate in severity. Identification of one case of hepatotoxicity might be of clinical relevance. In this context, the CHMP concluded that hepatotoxicity will be further monitored in the post-authorisation setting by means of routine pharmacovigilance activities including use of data capture aid for hepatotoxicity, collection of data in the ongoing study Fx1A-303 and collection of data on adverse events in the TTR-associated amyloidosis outcomes survey (THAOS).

These pharmacovigilance measures were deemed satisfactory by the CHMP to further characterize this potential risk.

The benefit-risk of tafamidis in ATTR-PN patients with non V30M mutation is based on an open label study and the data are therefore not robust. However, the applicant provided a comparison of the monthly rate of change on NIS before and after treatment with tafamidis and the CHMP agreed that this, together with the TTR stabilisation data, is supportive of the extrapolation from V30M to non V30M patients. In order to collect more information on the efficacy and safety of tafamidis in non V30M patients, the CHMP requested that a dedicated sub-study shall be performed by the applicant to further evaluate tafamidis safety in non V30M patients and to collect further clinical data on the patients´ neurologic status.

Discussion on the benefit-risk balance

The pivotal phase II/III study did not show statistically significant differences on the primary analysis, conducted with a conservative approach, i.e., with patients undergoing liver transplantation during the study considered as treatment failures. The other pre-specified and supplementary (with multiple imputations) analyses and results on secondary criteria showed statistically significant differences in favour of tafamidis. Furthermore, other supplementary analyses performed by the applicant, i.e. determination of yearly rate of progression of the disease and analyses of efficacy according to different thresholds for responders allowed to validate the clinical relevance of the effect.

The data on patient exposure showed that 308 individuals received at least one dose of tafamidis, 147 ATTR patients for at least 6 months, 113 for at least 12 months and 43 for at least 2 years. The safety of tafamidis, evaluated in the patients included in the studies and in healthy volunteers, is re-assuring and no strong signal seemed to emerge. The CHMP considered that identified risks will be monitored and are manageable in the post-authorisation setting as described in the Risk Management Plan. The CHMP also took into consideration that data from the THAOS registry with respect to the V30M mutation will be provided on an annual basis by the MAH; this is reflected in the RMP accordingly. In addition, the CHMP considered that treatment with tafamidis should be initiated by and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid polyneuropathy.

With respect to the benefit-risk balance in ATTR-PN patients including those with the rare (non-V30M) mutations, the CHMP pointed out that the clinical data on the rare mutations originated in an open (uncontrolled) setting and were thus not robust. However, at the same time the CHMP considered the data comparing the monthly rate of change on the NIS-LL score before and after treatment re-assuring and agreed that the mechanism of action together with the results of TTR stabilisation data (clinical pharmacology) were supportive of the extrapolation from V30M to non-V30M patients. In their review, the CHMP concluded that the dataset was sufficient to conclude on a positive benefit-risk balance of tafamidis in the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Taking into due consideration the rarity of the disease, the CHMP requested the marketing authorisation to be granted under exceptional circumstances. In particular, the CHMP took into account the fact that due to the rarity of the non-V30M patient population a standard double-blind placebo study is not feasible and that the applicant cannot be expected to provide comprehensive evidence. In this context, the CHMP concluded that the marketing authorisation under exceptional circumstances should be granted subject to a specific obligation to follow non-V30M patients in a proposed sub-study of the THAOS registry:

Specific obligation:

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

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by concensus that the risk-benefit balance of Vyndaqel in the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the medicinal product should follow the standard requirements until otherwise agreed by the CHMP.

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

The Marketing Authorisation Holder shall agree the format and content of the physician information leaflet with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Vyndaqel are provided with the healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Physician Information Leaflet

The Physician Information Leaflet should contain the following key messages:

- The need to counsel patients on important risks associated with Vyndaqel therapy and appropriate precautions when using the medicine, particularly the avoidance of pregnancy and the need for effective contraception.
- That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Vyndaqel since there is limited knowledge about the clinical safety due to the rare nature of transthyretin amyloidosis.
- That physicians are encouraged to enter patients in the Transthyretin Amyloidosis Outcome Survey (THAOS) and provided with details how to enroll patients into this international disease registry.
- The existence and scope of the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program and the details how to report pregnancies in women who are being treated with Vyndaqel.

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

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

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

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

The Member States shall agree the final educational material with the Marketing Authorization Holder (MAH) prior to launch of the product in their territory.

The Member States shall ensure that the MAH provides all physicians who are expected to prescribe or use Vyndaqel with a healthcare professional educational pack containing the following:

- The Summary of Product Characteristics
- The Physician Information Leaflet

The Physician Information Leaflet should contain the following key messages:

- The need to counsel patients on important risks associated with Vyndaqel therapy and appropriate precautions when using the medicine, particularly the avoidance of pregnancy and the need for effective contraception.
- That patients should be advised to contact their doctor about adverse events and that physicians/pharmacists should report suspected adverse reactions to Vyndaqel since there is limited knowledge about the clinical safety due to the rare nature of transthyretin amyloidosis.
- That physicians are encouraged to enter patients in the Transthyretin Amyloidosis Outcome Survey (THAOS) and provided with details how to enroll patients into this international disease registry.
- The existence and scope of the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program and the details how to report pregnancies in women who are being treated with Vyndaqel.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that tafamidis is to be qualified as a new active substance.