1. NAME OF THE MEDICINAL PRODUCT

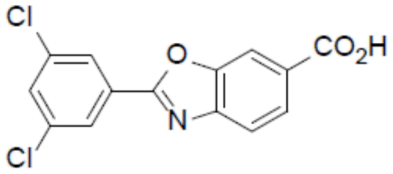
VYNDAMAX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VYNDAMAX is a soft gelatin capsule containing 61 mg micronised tafamidis.

Each soft capsule contains no more than 44 mg of sorbitol.

Chemical structure



3. PHARMACEUTICAL FORM

Soft gelatin capsule

Reddish brown, opaque, oblong (approximately 21 mm) capsule printed with “VYN 61” in white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VYNDAMAX is indicated for the treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation.

4.2 Posology and method of administration

Posology

The recommended dose of VYNDAMAX is 61 mg tafamidis orally once daily (see Section 5.1).

VYNDAMAX can be taken with or without food.

Special populations

Paediatric
VYNDAMAX should not be prescribed in the paediatric population as transthyretin amyloidosis is not a disease present in this population.

Elderly
No dosage adjustment is required for elderly patients (≥65 years) (see Section 5.2).

Renal or hepatic impairment
No dosage adjustment is required for patients with renal impairment, or mild or moderate hepatic impairment. VYNDAMAX has not been studied in patients with severe hepatic impairment.

Method of administration

Oral use.

The capsule(s) should be swallowed whole and not crushed or cut. VYNDAMAX may be taken with or without food.

If a dose is missed, the patient should take the dose as soon as remembered. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the regularly scheduled time. Do not double the dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of VYNDAMAX (see Section 6.1).

4.4 Special warnings and precautions for use

Studies in animals have shown developmental toxicity (see Section 5.3). The potential risk for humans is unknown. VYNDAMAX is not recommended during pregnancy. Women of childbearing potential should use appropriate contraception when taking VYNDAMAX and continue to use appropriate contraception for 1-month after stopping treatment with VYNDAMAX (see Section 4.6).

A study has not been conducted in organ transplant patients. The efficacy and safety of VYNDAMAX in organ transplant patients has not been established.

Based on the potential of VYNDAMAX to inhibit the efflux transporter BCRP (breast cancer resistant protein), caution should be used when co-administering VYNDAMAX and BCRP substrates, because of the risk of BCRP substrate related adverse reactions (see Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical study in healthy volunteers, tafamidis did not induce or inhibit the cytochrome P450 enzyme CYP3A4.

In vitro data also indicated that tafamidis does not significantly inhibit cytochrome P450 enzymes CYP1A2, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In addition, tafamidis did not induce CYP1A2, but did induce CYP2B6 *in vitro*, however based on the negative clinical CYP3A4 induction results, it can be concluded that the likelihood of CYP2B6 clinical induction is low.

In vitro studies suggest that it is unlikely tafamidis will cause drug interactions at clinically relevant concentrations with substrates of UDP-glucuronosyltransferase (UGT) systemically. Tafamidis may inhibit intestinal activities of UGT1A1.

Tafamidis showed a low potential to inhibit Multi-Drug Resistant Protein (MDR1) (also known as P-glycoprotein; P-gp) systemically and in the gastrointestinal (GI) tract, organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 (MATE1) and MATE2K, organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 at clinically relevant concentrations.

Tafamidis has the potential to inhibit the efflux transporter BCRP and may increase systemic exposure of substrates of this transporter (e.g., methotrexate, rosuvastatin, atorvastatin, apixaban, rivaroxaban, imatinib). In a clinical study in healthy participants, the exposure of BCRP substrate rosuvastatin increased approximately 2-fold following multiple doses of 61 mg tafamidis daily dosing. Dose adjustment may be needed for these substrates.

Patients should be carefully monitored for BCRP substrate related adverse reactions when used concomitantly with VYNDAMAX. A dose modification of the BCRP substrate according to its Prescribing Information should be considered.

Tafamidis may have the potential to inhibit organic anion transporter 1 (OAT1) and may cause drug-drug interactions with substrates of this transporter (e.g., non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). However, additional risk assessments based on the R-value model ($AUCi/AUC = 1+(C_{max},u/Ki)$) were performed and the maximal predicted change in AUC of OAT1 substrates was determined to be less than 1.25 for the 20 mg tafamidis meglumine daily dose, 80 mg tafamidis meglumine daily dose, and 61 mg tafamidis daily dose, therefore, inhibition of OAT1 transporter by tafamidis is not expected to result in clinically significant interactions.

Tafamidis does not inhibit the organic anion transporter 3 (OAT3). In a clinical study in healthy participants, the renal clearance of the OAT3 substrate rosuvastatin did not change following multiple doses of 61 mg tafamidis daily dosing.

Patients receiving substrates of both BCRP and OAT with tafamidis should be assessed as exposure of these drugs may be increased e.g., methotrexate AUC might be increased by ~50%.

No interaction studies have been performed evaluating the effect of other medicinal products on tafamidis.

<u>Laboratory test abnormality</u>

Tafamidis may decrease serum concentrations of total thyroxine, without an accompanying change in free thyroxine (T4) or thyroid stimulating hormone (TSH). This observation in total thyroxine values may likely be the result of reduced thyroxine binding to or displacement from transthyretin (TTR) due to the high binding affinity tafamidis has to the TTR thyroxine receptor. No corresponding clinical findings consistent with thyroid dysfunction have been observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

VYNDAMAX is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no adequate data on the use of VYNDAMAX in pregnant women. Studies in animals have shown developmental toxicity (see Section 5.3). The potential risk for humans is unknown. VYNDAMAX is not recommended during pregnancy.

To monitor outcomes of pregnant women exposed to VYNDAMAX, a Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program has been established. If a pregnancy occurs in a woman being treated with VYNDAMAX, medical or healthcare professionals are encouraged to report the pregnancy by contacting the Marketing Authorisation Holder's local office.

Breastfeeding

Nonclinical data demonstrate that tafamidis is secreted in the milk of lactating rats. While the effect of VYNDAMAX on nursing infants after administration to the mother has not been studied, a risk to infants cannot be excluded. Breastfeeding is not recommended during treatment with VYNDAMAX.

Fertility

There were no effects of tafamidis on fertility, reproductive performance or mating behaviour in the rat at any dose (see Section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of VYNDAMAX on the ability to drive or use machines have been performed.

4.8 Undesirable effects

The data across clinical trials reflect exposure of 377 transthyretin amyloid cardiomyopathy (ATTR-CM) patients to either 20 mg or 80 mg (administered as four 20 mg capsules) of tafamidis meglumine daily for an average of 24.5 months (ranging from 1 day to 111 months).

Adverse events were assessed from ATTR-CM clinical trials with tafamidis meglumine including a 30-month placebo-controlled trial in patients diagnosed with ATTR-CM (see

Section 5.1). The frequency of adverse events in patients treated with 20 mg or 80 mg tafamidis meglumine was similar and comparable to placebo.

A lower proportion of tafamidis meglumine-treated patients compared to placebo discontinued due to an adverse event in the 30-month placebo-controlled trial in patients diagnosed with ATTR-CM [40 (22.7%), 16 (18.2%), and 51 (28.8%) from the tafamidis meglumine 80 mg (administered as four 20 mg capsules), tafamidis meglumine 20 mg, and placebo groups, respectively].

An adverse reaction of diarrhoea was identified post-marketing in the ATTR-CM population and is listed below by MedDRA System Organ Class (SOC).

Table 1: Adverse drug reactions by SOCs and CIOMS frequency category listed by decreasing medical seriousness or clinical importance within each frequency category and SOC, identified in the ATTR-CM population

System Organ Class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000	Frequency not known (cannot be estimated from the available data)
Gastrointestinal disorders		Diarrhoea*				

* Adverse Drug Reaction (ADR) identified post-marketing.

4.9 Overdose

There is minimal clinical experience with overdose. During clinical trials, two patients diagnosed with ATTR-CM accidentally ingested a single tafamidis meglumine dose of 160 mg without the occurrence of any associated adverse events. The highest dose of tafamidis meglumine* given to healthy volunteers in a clinical trial was 480 mg as a single dose. There was one reported treatment-related adverse event of mild hordeolum at this dose.

* A single 61 mg tafamidis capsule is bioequivalent to 80 mg tafamidis meglumine (four 20 mg tafamidis meglumine capsules). The two formulations are not interchangeable on a per mg basis (see Sections 5.1 and 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tafamidis is a selective stabiliser of TTR. Tafamidis binds with negative cooperativity to the two thyroxine binding sites on the native tetrameric form of TTR preventing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of TTR tetramer dissociation forms the rationale for the use of VYNDAMAX to reduce all-cause mortality and cardiovascular-related hospitalisation in ATTR-CM patients.

A TTR stabilisation assay was utilised as a pharmacodynamic marker and assessed the stability of the TTR tetramer under denaturation conditions. The TTR stabilisation assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre- and

post-treatment with 2-day *in vitro* denaturation with urea. Using this assay, a dose-dependent trend for greater TTR tetramer stabilisation is observed for tafamidis meglumine 80 mg compared to tafamidis meglumine 20 mg. However, the clinical relevance of a higher TTR tetramer stabilisation towards cardiovascular outcomes is not known.

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

A population PK/PD analysis was conducted with a database consisting of 3662 observations from 102 healthy subjects and 558 patients with transthyretin amyloidosis.

None of the following parameters were found to modify the VYNDAMAX pharmacodynamic response: race (non-Japanese vs. Japanese), patient type (healthy volunteer, ATTR-PN, ATTR-CM), or genotype.

Clinical studies

Efficacy was demonstrated in a multicentre, international, double-blind, placebo-controlled, randomised 3-arm study in 441 patients with wild-type or hereditary ATTR-CM.

Patients were randomised to either tafamidis meglumine 20 mg (n=88) or 80 mg [administered as four 20 mg tafamidis meglumine capsules] (n=176) or matching placebo (n=177) once daily, in addition to standard of care (e.g., diuretics) for 30 months. Tafamidis meglumine 80 mg is bioequivalent to tafamidis 61 mg (see Section 5.2). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as by baseline severity of disease (NYHA Class). Table 2 describes the patient demographics and baseline characteristics. Patients with NYHA Class IV were excluded from the study.

Table 2: Patient demographics and baseline characteristics

Characteristic	**Pooled Tafamidis N=264**	**Placebo N=177**
Age — year		
Mean (standard deviation)	74.5 (7.2)	74.1 (6.7)
Median (minimum, maximum)	75 (46, 88)	74 (51, 89)
Sex — number (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
TTR genotype — number (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
NYHA Class — number (%)		
NYHA Class I	24 (9.1)	13 (7.3)
NYHA Class II	162 (61.4)	101 (57.1)
NYHA Class III	78 (29.5)	63 (35.6)
Race — number (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)

Characteristic	Pooled Tafamidis N=264	Placebo N=177
Other	3 (1.1)	0

Abbreviations: ATTRm=variant transthyretin amyloid, ATTRwt=wild-type transthyretin amyloid, NYHA=New York Heart Association.

The primary analysis used a hierarchical combination applying the method of Finkelstein-Schoenfeld (F-S) to all-cause mortality and frequency of cardiovascular-related hospitalisations, which is defined as the number of times a subject is hospitalised (i.e., admitted to a hospital) for cardiovascular-related morbidity. The method compared each patient to every other patient within each stratum in a pair-wise manner that proceeded in a hierarchical fashion using all-cause mortality followed by frequency of cardiovascular-related hospitalisations when patients could not be differentiated based on mortality.

This analysis demonstrated a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalisations in the pooled 20 mg and 80 mg tafamidis dose group versus placebo (Table 3).

Table 3: Primary analysis using Finkelstein-Schoenfeld (F-S) Method of all-cause mortality and frequency of cardiovascular-related hospitalisations

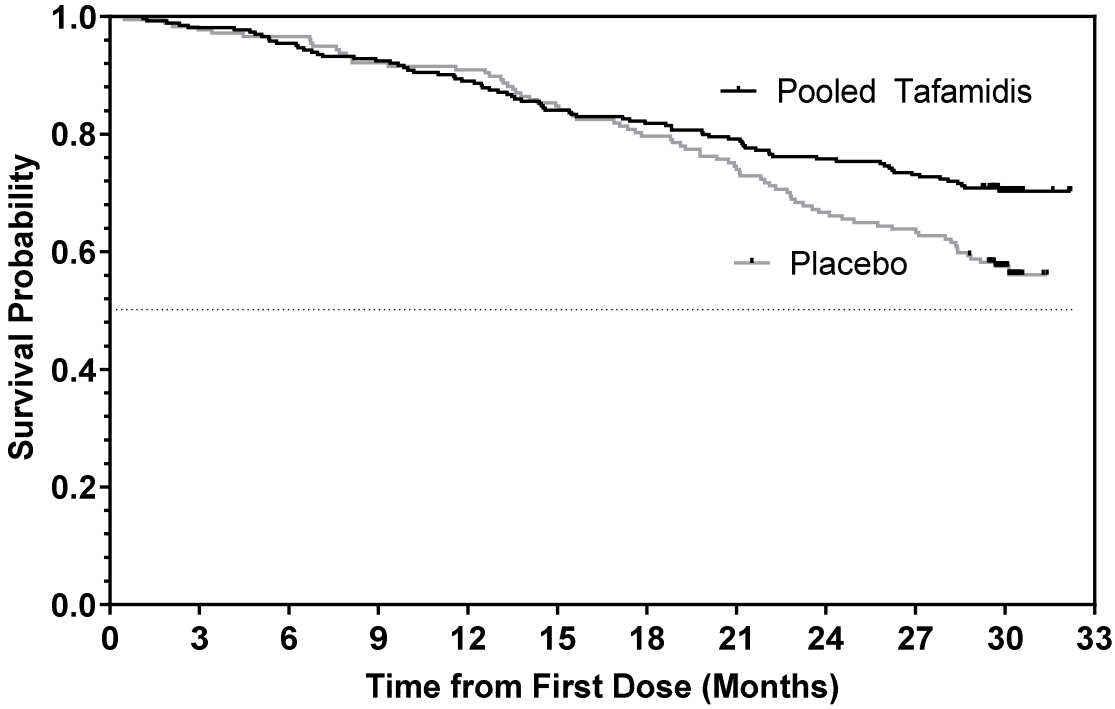
Primary Analysis	Pooled Tafamidis N=264	Placebo N=177
Number (%) of subjects alive* at Month 30	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalisations during 30 months (per patient per year) among those alive at Month 30†	0.297	0.455
p-value from F-S Method	0.0006	

* Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these subjects are treated in the analysis as equivalent to death. Therefore, such subjects are not included in the count of "Number of subjects alive at Month 30" even if such subjects are alive based on 30 month vital status follow-up assessment.
† Descriptive mean among those who survived the 30 months.

Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalisation) also demonstrated significant reductions for tafamidis versus placebo.

The hazard ratio from the all-cause mortality Cox-proportional hazard model for pooled tafamidis was 0.698 (95% CI 0.508, 0.958), indicating a 30.2% reduction in the risk of death relative to the placebo group (p=0.0259). A Kaplan-Meier plot of time to event all-cause mortality is presented in Figure 1.

Figure 1: All-cause mortality*



Subjects Remaining at Risk (Cumulative events)												
Pooled	264	259	252	244	235	222	216	209	200	193	99	0
Tafamidis	0	5	12	20	29	42	48	55	64	71	78	78
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

* Heart transplants and cardiac mechanical assist devices treated as death. Hazard ratio from Cox-proportional hazards model with treatment, TTR genotype (variant and wild-type), and New York Heart Association (NYHA) Baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

There were significantly fewer cardiovascular-related hospitalisations with tafamidis compared with placebo with a reduction in risk of 32.4% (Table 4).

Table 4: Cardiovascular-related hospitalisation frequency

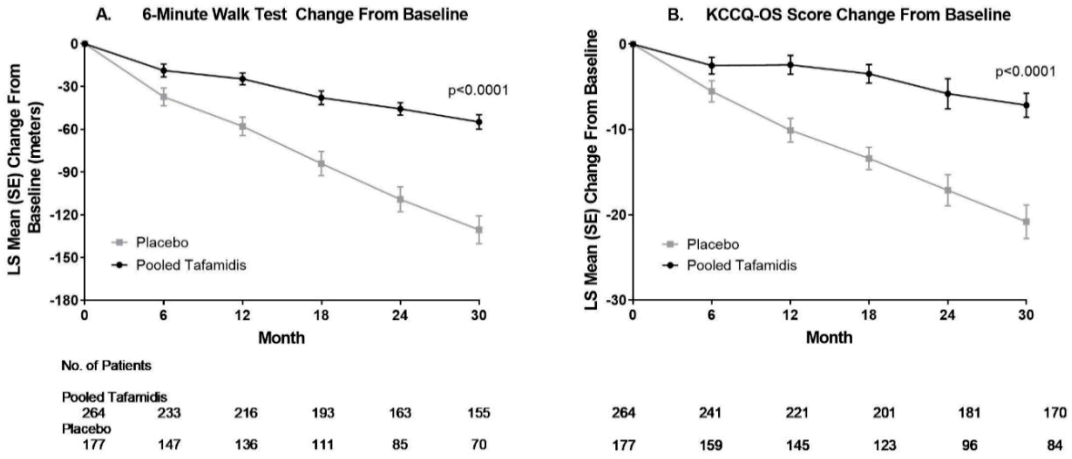
	Pooled Tafamidis N=264	**Placebo N=177**
Total (%) number of subjects with cardiovascular-related hospitalisations	138 (52.3)	107 (60.5)
Cardiovascular-related hospitalisations per year*	0.4750	0.7025
Pooled tafamidis versus placebo treatment difference (relative risk ratio [95% CI])*	0.6761 (0.5639, 0.8107)	
p-value*	<0.0001	

Abbreviation: NYHA=New York Heart Association.

* This analysis was based on a Poisson regression model with treatment, TTR genotype (variant and wild-type), New York Heart Association (NYHA) Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors.

The treatment effects of tafamidis on functional capacity and health status were assessed by the 6-Minute Walk Test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively. A significant treatment effect favouring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score (Figure 2 and Table 5).

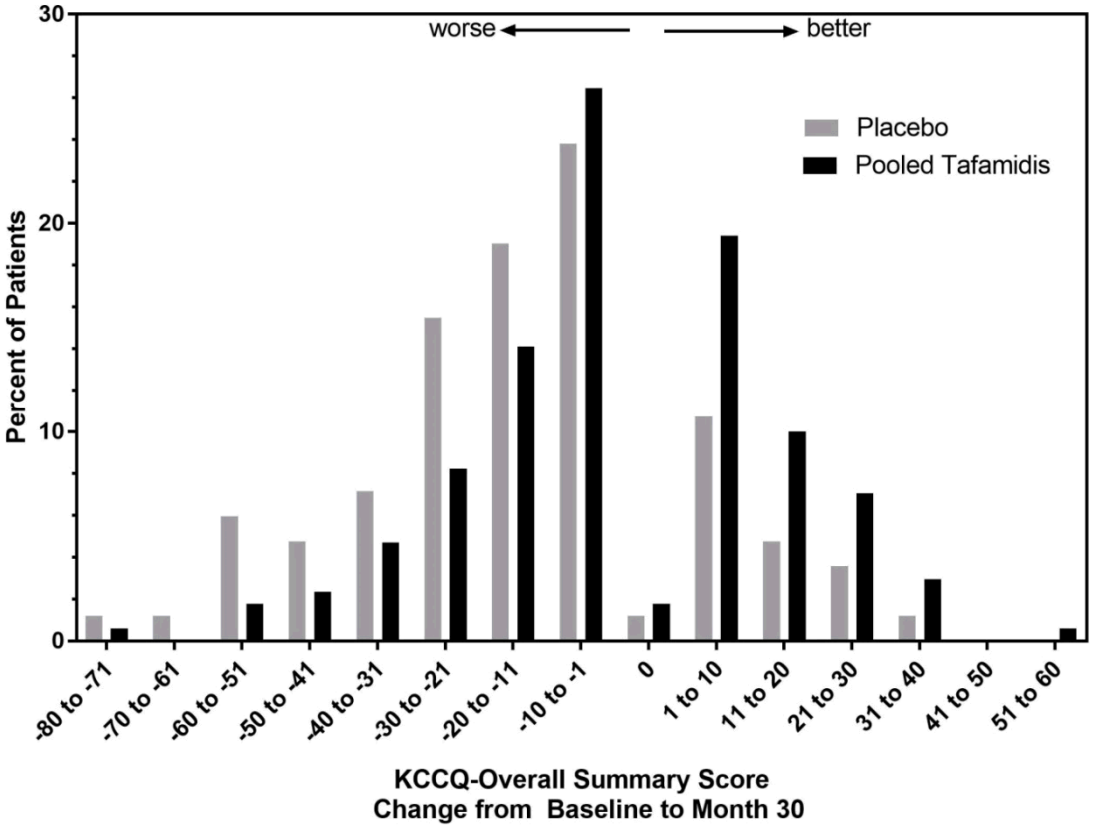
Figure 2: Change from Baseline to Month 30 in 6MWT distance and KCCQ-OS score



Abbreviations: 6MWT=6-Minute Walk Test, KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.
Panel A shows change from Baseline to Month 30 in pooled tafamidis compared with placebo treated patients in 6MWT distance.
Panel B shows change from Baseline to Month 30 in pooled tafamidis compared with placebo treated patients in KCCQ-OS score.

The KCCQ-OS score is composed of four domains including Total Symptom (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. All four domains significantly favoured tafamidis compared to placebo at Month 30 (Figure 2 and Table 5). KCCQ-OS and domain scores range from 0-100 with higher scores representing better health status. The cumulative distribution and distribution for change from Baseline to Month 30 for KCCQ-OS show that the proportion of patients with declining KCCQ-OS scores was lower for the pooled tafamidis treated group compared to placebo (Figure 3).

Figure 3: Histogram of change from Baseline to Month 30 in KCCQ-OS



Abbreviation: KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary.

Table 5: 6MWT and KCCQ-OS and component domain scores

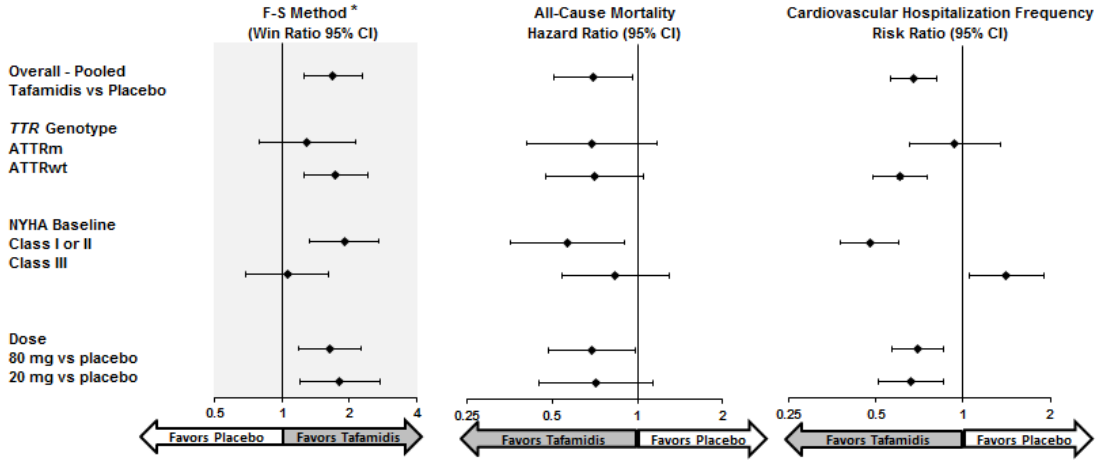
Endpoints	Baseline Mean (SD)		Change from Baseline to Month 30, LS Mean (SE)		Treatment difference from placebo LS Mean (95% CI)	p-value
	Pooled Tafamidis N=264	Placebo N=177	Pooled Tafamidis	Placebo		
6MWT (meters)	350.55 (121.30)	353.26 (125.98)	-54.87 (5.07)	-130.55 (9.80)	75.68 (57.56, 93.80)	*p*<0.0001
KCCQ-OS	67.27 (21.36)	65.90 (21.74)	-7.16 (1.42)	-20.81 (1.97)	13.65 (9.48, 17.83)	*p*<0.0001
KCCQ-TS	73.45 (20.27)	72.11 (20.64)	-6.26 (1.36)	-18.75 (2.31)	12.48 (8.13, 16.84)	*p*<0.0001
KCCQ-SF	73.42 (21.85)	70.90 (22.49)	-6.53 (1.44)	-19.37 (2.66)	12.85 (7.30, 18.39)	*p*<0.0001
KCCQ-SB	73.58 (20.72)	73.31 (20.82)	-6.04 (1.50)	-17.91 (2.34)	11.87 (7.75, 16.00)	*p*<0.0001
KCCQ-PL	69.07 (22.77)	68.24 (24.18)	-9.98 (1.33)	-22.62 (2.21)	12.64 (8.54, 16.75)	*p*<0.0001
KCCQ-QL	62.63 (24.73)	59.98 (24.65)	-1.53 (1.83)	-15.94 (2.38)	14.40 (9.07, 19.74)	*p*<0.0001
KCCQ-SL	63.36 (28.96)	63.10 (28.97)	-8.79 (2.09)	-24.66 (2.92)	15.87 (10.34, 21.40)	*p*<0.0001

Abbreviations: 6MWT=6-Minute Walk Test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS=least squares; CI=confidence interval; TS=Total Symptom; SF=Symptom Frequency; SB=Symptom Burden; PL=Physical Limitation; QL=Quality of Life; SL=Social Limitation.

In the pivotal study, patients who exhibited >32% TTR stabilization were considered stabilised. At Month 1, a significantly greater proportion of patients in the pooled tafamidis group (211/245 [86.1%] patients) demonstrated TTR stabilisation than was observed for patients in the placebo group (6/170 [3.5%] patients) (p<0.0001).

Results from F-S method represented by win ratio for the combined endpoint and its components (all-cause mortality and frequency of cardiovascular-related hospitalisation) consistently favoured tafamidis versus placebo across all subgroups (wild-type, variant and NYHA Class I & II, and III) except for cardiovascular-related hospitalisation frequency in NYHA Class III (Figure 4). Win ratio is the number of pairs of treated-patient "wins" divided by number of pairs of placebo patient "wins". Analyses of 6MWT and KCCQ-OS also favoured tafamidis relative to placebo within each subgroup.

Figure 4: Results from F-S Method and components by subgroup and dose



Abbreviations: ATTRm=variant transthyretin amyloid, ATTRwt=wild-type transthyretin amyloid, F-S=Finkelstein Schoenfeld, CI=Confidence Interval.
* F-S results presented using win ratio (based on all-cause mortality and frequency of cardiovascular hospitalisation).
Heart transplants and cardiac mechanical assist devices treated as death.

In applying the F-S method to each dose group individually, tafamidis reduced the combination of all-cause mortality and frequency of cardiovascular-related hospitalisations for both the 80 mg and 20 mg doses compared to placebo (p=0.0030 and p=0.0048, respectively).

Results of the components of the primary analysis, functional capacity and health status (6MWT and KCCQ-OS at Month 30), cardiovascular-related mortality, and TTR stabilisation at Month 1 were analysed by individual doses (80 mg and 20 mg) compared to placebo. The comparison of each dose versus placebo demonstrated an effect with tafamidis for all analyses. The observed results were similar for subjects treated with either the tafamidis meglumine 80 mg or 20 mg doses.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) differentiated between the 80 mg and the 20 mg doses. For NT-proBNP, the LS mean difference in change from

Baseline to Month 30 from placebo for 20 mg tafamidis meglumine was -1417.02 pg/mL (SE=743.38) and for 80 mg was -2587.54 pg/mL (SE=570.25). Further, the LS mean difference between the 20 mg and 80 mg doses was 1170.51 pg/mL (SE=587.31) (p=0.0468), favouring the 80 mg dose group. Similar results were observed for Troponin I where the LS mean difference in change from Baseline to Month 30 from placebo for tafamidis meglumine 20 mg was -0.06 ng/mL (SE=0.045) and for 80 mg was -0.10 ng/mL (SE=0.018). The LS mean difference between the 20 mg and 80 mg doses for Troponin I was 0.05 ng/mL (SE=0.04) (p=0.2479), numerically favouring the 80 mg dose group, although the trend did not reach statistical significance.

In an ongoing extension study, patients who completed 30 months of blinded treatment in the pivotal study were eligible to continue to receive 20 mg or 80 mg tafamidis meglumine. Dose blind was maintained during this extension phase. As of February 2018, the median duration of treatment was approximately 36 months. In a post-hoc comparison of all-cause mortality in the extension study by dose, the Hazard Ratio was 0.8976 (95% CI 0.5711, 1.4108), suggesting a 10.2% reduction in risk of death in patients receiving 80 mg relative to patients receiving 20 mg, but this difference was not statistically significant (p=0.6395).

A supra-therapeutic, single, 400 mg oral dose of tafamidis meglumine solution in healthy volunteers demonstrated no effect on the QTc interval.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of VYNDAMAX was determined in Phase I studies in healthy volunteers and patients with ATTR-PN or ATTR-CM.

Absorption

After oral administration of VYNDAMAX once daily, the maximum peak concentration (C_{max}) is achieved at a median time (t_{max}) within 4 hours after dosing in the fasted state. Concomitant administration of a high fat, high calorie meal altered the rate of absorption, but not the extent of absorption. These results support the administration of VYNDAMAX with or without food.

Distribution

Tafamidis is highly protein bound (>99%) in plasma. The apparent steady-state volume of distribution is 16 litres for tafamidis meglumine and 18.5 litres for tafamidis, based on 75 kg adult.

Metabolism and excretion

While there is no explicit evidence of biliary excretion of tafamidis in humans, based on preclinical data, it is suggested that tafamidis is metabolised by glucuronidation and excreted via the bile. This route of metabolism and excretion is likely in humans, as approximately 59% of the total administered dose is recovered in faeces mostly as unchanged drug, and approximately 22% recovered in urine mostly as the glucuronide metabolite. Based on population pharmacokinetic results, the apparent oral clearance of tafamidis meglumine is 0.228 L/h (0.263 L/h for tafamidis) and the population mean half-life is approximately 49 hours.

Dose and time linearity

Exposure from once-daily dosing with tafamidis meglumine increased with increasing dose up to 480 mg single dose and multiple doses up to 80 mg per day. In general, increases were proportional or near proportional to dose.

Tafamidis 61 mg provides steady-state exposures (C_{max} and AUC) equivalent to 80 mg tafamidis meglumine (administered as four 20 mg capsules), which was administered to patients with ATTR-CM in the double-blind, placebo-controlled, randomised study (Table 6) (see Section 5.1).

Table 6: Comparative pharmacokinetics of tafamidis 61 mg capsule to tafamidis meglumine administered as four 20 mg capsules

Parameter (units)	Comparison (test versus reference)	Adjusted geometric means		Test versus reference	
		Test	Reference	Ratio (%)[a] (test/reference)	90% CI[a] for ratio
AUC_{tau} (µg.h/mL)	Tafamidis 61 mg capsule (Test) versus Tafamidis meglumine Four 20 mg capsules (Reference)	170.0	166.2	102.28	(97.99, 106.76)
C_{max} (µg/mL)		8.553	9.087	94.12	(89.09, 99.42)

Abbreviations: CI=confidence interval; mg=milligram; µg=microgram; mL=millilitre; h=hour; AUC_{tau}=area under curve from time 0 to time tau, the dosing interval, where tau=24 hours for daily dosing; C_{max}=maximum serum concentration.

[a] The ratios and 90% CIs are expressed as percentages.

Mean half-life and oral clearance were similar after single and repeated administration of a 20 mg dose of tafamidis meglumine, indicating a lack of induction or inhibition of tafamidis metabolism.

Results of once-daily dosing with tafamidis meglumine 15 mg to 60 mg oral solution for 14 days demonstrated that steady-state (ss) was achieved by Day 14.

Drug interactions

No significant effect was observed on the pharmacokinetics of midazolam (a CYP3A4 substrate) or on the formation of its active metabolite (1-hydroxymidazolam), when a single 7.5 mg dose of midazolam was administered prior to and after a 14-day regimen of 20 mg once-daily tafamidis meglumine. The overall systemic exposure ($AUC_{0-\infty}$) and total clearance (CL/F) of midazolam were shown to be equivalent. In addition, tafamidis did not induce CYP3A4 activity in either male or female subjects.

Pharmacokinetics in special patient groups

Elderly patients: Based on population pharmacokinetic results, patients ≥65 years of age had an average 15% lower estimate of apparent oral clearance at steady-state when compared with patients under the age of 65. However, the difference in clearance results in <20%

increases in mean C_{max} and AUC compared to younger subjects and is not clinically significant.

Renally impaired patients: VYNDAMAX has not specifically been evaluated in patients with renal impairment. Tafamidis is primarily metabolised by glucuronidation and is likely excreted via the hepatobiliary pathway. The influence of creatinine clearance on tafamidis pharmacokinetics (PK) was evaluated in a population PK analysis in patients with creatinine clearance >18 mL/min. Pharmacokinetic estimates indicated no difference in apparent oral clearance of tafamidis in patients with creatinine clearance <80 mL/min compared to those with creatinine clearance ≥80 mL/min. No dosage adjustment is required in patients with renal impairment. Limited data are available in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

Hepatically impaired patients: No dose adjustment is necessary in mild or moderate hepatic impairment. Pharmacokinetic data indicated decreased systemic exposure (approximately 40%) and increased total clearance (0.52 L/h versus 0.31 L/h) of tafamidis meglumine in subjects with moderate hepatic impairment (Child-Pugh Score of 7-9 inclusive) compared to healthy subjects. As TTR levels are lower in patients with moderate hepatic impairment than in healthy subjects, the exposure of VYNDAMAX relative to the amount of TTR would be sufficient for stabilisation of the TTR tetramer in these patients. Exposure to VYNDAMAX was similar between subjects with mild hepatic impairment and healthy subjects.

The exposure to VYNDAMAX in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Fertility

There were no effects of tafamidis meglumine on fertility, reproductive performance, or mating behaviour in the rat at any dose. Rats were dosed daily (5, 15, and 30 mg/kg/day) prior to cohabitation (for at least 15 days for females and 28 days for males), throughout the cohabitation period to the day prior to termination of males and through to implantation of females (Gestation Day 7). No adverse effects were noted on male rats in toxicity, fertility and mating behaviour at any dose. Because no reproductive effects occurred at the highest dose tested, the paternal and maternal no observed effect level for reproductive toxicity of tafamidis meglumine is greater than 30 mg/kg/day (9.5 times the clinical AUC at the maximum recommended human dose [MRHD] of 61 mg tafamidis per day, and estimated to be greater than 9.7 times the clinical AUC at the MRHD of 80 mg tafamidis meglumine per day).

Developmental toxicity

In pregnant rabbits increased skeletal variations were observed at ≥0.5 mg/kg/day (exposures approximately equivalent to the clinical exposures at the MRHD of 61 mg tafamidis and 80 mg tafamidis meglumine respectively), while increased skeletal malformations, reduced embryo-foetal survival and reduction in foetal body weights were observed at 8 mg/kg/day (AUC exposures ≥9.1 times and 9.3 times clinical AUC at the MRHD of 61 mg tafamidis and 80 mg tafamidis meglumine respectively). In pregnant rats, oral administration of tafamidis (15, 30, and 45 mg/kg/day) from Gestation Day 7 through 17 resulted in decreased foetal

weights at ≥30 mg/kg/day (approximately ≥9.5 times and ≥9.7 times the human AUC at the clinical dose of 61 mg tafamidis and 80 mg tafamidis meglumine respectively).

In the rat pre- and post-natal development study with tafamidis, pregnant rats were orally administered tafamidis meglumine at doses of 5, 15, or 30 mg/kg/day from Gestation Day 7 through Lactation Day 20. Decreased pup survival, reduced pup weights and malformations (microphthalmia, enophthalmos, domed head) were noted at doses ≥15 mg/kg/day (≥6.4 times and ≥6.6 times the clinical AUC at the MRHD of 61 mg tafamidis and 80 mg tafamidis meglumine per day respectively). Decreased pup weights in males were associated with delayed sexual maturation (preputial separation) at 15 mg/kg/day. Impaired performance in a water-maze test for learning and memory was observed at 15 mg/kg/day. The no observable adverse effect level (NOAEL) for viability and growth in the F1 generation offspring following maternal exposures to tafamidis was 5 mg/kg/day (human equivalent dose of 0.8 mg/kg/day), a dose approximately 0.92 times and 1.2 times the clinical dose of 61 mg tafamidis and 80 mg tafamidis meglumine respectively for a 70 kg adult.

Genotoxicity

Tafamidis was not genotoxic in a bacterial reverse mutation assay, in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus test. Nonclinical data demonstrated no special hazard for humans based on conventional studies of genotoxicity.

Carcinogenicity

There was no evidence of increased incidence of neoplasia in a 2-year carcinogenicity study in rats at exposures up to 18 times the human AUC at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine. There was no evidence of an increased incidence of neoplasia in the transgenic (Tg)-rasH2 mouse following repeat daily administration for 26 weeks at exposures up to 9.6 times and 9.9 times the human AUC at the clinical doses of 61 mg tafamidis and 80 mg tafamidis meglumine respectively. In this study, significant non neoplastic lesions were noted in the kidneys (nephrosis) and liver (centrilobular hypertrophy and single cell necrosis) in the Tg-rasH2 mice at dose levels ≥2.8 times and ≥2.9 times the clinical AUC at 61 mg tafamidis and 80 mg tafamidis meglumine respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content:
Polyethylene Glycol 400
Polysorbate 20
Povidone (K-value 90)
Butylated Hydroxytoluene

Capsule Shell:
Gelatin (195 Acid Type)
Sorbitol Special-Glycerin Blend
Purified Water
Iron Oxide, Red

Purified Water

Printing Ink (Ink, White Opacode):
Alcohol SDA 35A
Ammonium Hydroxide 28%
Isopropyl Alcohol
Purified Water
Polyethylene Glycol (Macrogol MW400)
Polyvinyl Acetate Phthalate
Propylene Glycol
Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The drug product is packaged in a unit dose blister system utilising Polyvinyl Chloride/Aluminum Foil/Oriented Polyamide/Polyvinyl Chloride (PVC/Aluminum/oPA/PVC) with Aluminum Foil with heat seal coating as the lidding foil.

Pack Sizes

10 soft gelatin capsules x 3 blisters

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

VYN-SIN-0825/0
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