




# Application for the assessment of tafamidis for wild-type transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)

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# Abbreviations

AE	Adverse event
AIC	Akaike's information criteria
ATTR	Transthyretin-mediated amyloidosis
ATTR-ACT	Tafamidis in Transthyretin Cardiomyopathy Clinical Trial
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRm	Variant (mutant) transthyretin amyloid*
ATTRwt	Wild-type transthyretin amyloid*
BIC	Bayesian information criterion
BMI	Body mass index
cTTO	Composite time trade-off
CUA	Cost-utility analysis
CV	Cardiovascular
DCE	Discrete-choice experiments
DMC	Danish Medicines Council
EQ-5D-3L	European Quality of Life 5 Dimensions 3-Levels
EQ-5D-5L	European Quality of Life 5 Dimensions 5-Levels
EQ-VAS	European Quality Visual Analog Scale
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost effectiveness ratio
INR	International normalized ratio
ITT	Intention-to-treat
KCCQ	Kansas city cardiomyopathy questionnaire
KM	Kaplan-Meier
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NYHA	New York Heart Association
OS	Overall survival
PPP	Pharmacy purchasing price
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
RCT	Randomized controlled trial



TEAE Treatment emergent adverse events

*TTR* Transthyretin gene

WTP Willingness-to-pay

\*For convenience and readability, the abbreviations ATTRm and ATTRwt are used throughout the document to refer to the *TTR* genotype as well as the disease hereditary and wild-type ATTR-CM, respectively.



# 1. Regulatory information on the medicine

## Overview of the medicine

<b>Proprietary name</b>	Vyndaqel®
<b>Generic name</b>	Tafamidis
<b>Therapeutic indication as defined by EMA</b>	Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)
<b>Marketing authorization holder in Denmark</b>	Pfizer, Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
<b>ATC code</b>	N07XX08
<b>Combination therapy and/or co-medication</b>	Not applicable
<b>(Expected) Date of EC approval</b>	December 13, 2019
<b>Has the medicine received a conditional marketing authorization?</b>	No.  Tafamidis has, however, received an authorization under “exceptional circumstances”, and EMA has therefore reviewed new information on an annual basis.
<b>Accelerated assessment in the European Medicines Agency (EMA)</b>	No.
<b>Orphan drug designation (include date)</b>	No. The designation was withdrawn in November 2021 at the end of the 10-year period of market exclusivity.
<b>Other therapeutic indications approved by EMA</b>	Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (November 16, 2011).
<b>Other indications that have been evaluated by the DMC (yes/no)</b>	Yes - Vyndaqel has been evaluated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.
<b>Dispensing group</b>	BEGR



### Overview of the medicine

<b>Packaging – types, sizes/number of units and concentrations</b>	Pack size: a pack of 30 x 1 soft capsules. Each soft capsule contains 61 mg of micronized tafamidis.
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## 2. Summary table

### Summary

<b>Therapeutic indication relevant for the assessment</b>	Wild-type transthyretin amyloidosis in adult patients with cardiomyopathy (ATTRwt)
<b>Dosage regimen and administration</b>	The recommended dose of tafamidis for patients with ATTR-CM is 61 mg taken orally once daily.
<b>Choice of comparator</b>	Placebo
<b>Prognosis with current treatment (comparator)</b>	<p>Transthyretin-mediated amyloidosis (ATTR) is a life-threatening disease caused by the misfolding of transthyretin and its deposit as amyloid fibrils in various tissues, including the peripheral nervous system, the heart, the central nervous system and the eyes. Deposit in heart tissue may lead to ATTR-CM.</p> <p>In both the hereditary and wild-type form of ATTR-CM, the progressive nature of the disease and severe symptoms result in reduced quality of life and shortened lifespan.</p> <p>The degree of heart failure symptoms is traditionally described in terms of four New York Heart Association (NYHA) functional classes based on patient symptoms. Patients in NYHA functional class I-II, who experience none or few limitations in normal physical activities, may live a good life. Patients in NYHA functional class III and IV however, are significantly limited in their physical activity and experience symptoms at sedentary activities, such as shortness of breath or even while lying down (class IV). These patients have problems coping with everyday tasks. Mortality among heart failure patients increases proportionally with the increase in NYHA class.</p>
<b>Type of evidence for the clinical evaluation</b>	The pivotal phase III RCT vs. placebo (ATTR-ACT), and its long-term extension (LTE) study is used as evidence for the clinical evaluation.
<b>Most important efficacy endpoints (Difference/gain compared to comparator)</b>	Please see the original application for details on all endpoints. In the current application, only the endpoint overall survival (OS) is included.



**Summary**

**ATTRwt patients:** All-cause mortality was 40.3% and 59.7% in the continuous tafamidis group and the placebo to tafamidis group, respectively (HR: 0.61 [95% CI, 0.43–0.87]; p=0.006, favoring continuous tafamidis treatment) (data cut-off: March 2020 (1)).

**NYHA class I/II** (ATTRwt and ATTRm patients): All-cause mortality was 41% and 61% in the continuous tafamidis group and the placebo to tafamidis group, respectively (HR: 0.50 [95% CI: 0.35–0.73]; p=0.0003, favoring continuous tafamidis treatment) (data cut-off: August 2021 (2)).

**NYHA class III** (ATTRwt and ATTRm patients): All-cause mortality was 64% and 81% in the continuous tafamidis group and the placebo to tafamidis group, respectively (HR: 0.64 [95% CI: 0.41–0.99]; p=0.0460, favoring continuous tafamidis treatment) (data cut-off: August 2021 (2)).

**Most important serious adverse events for the intervention and comparator** Please see the original application for a list of serious adverse events and their frequencies in the ATTR-ACT study.  
In the current application, a list of adverse events reported for patients receiving continuous treatment with tafamidis in the ATTR-ACT LTE study is provided in section 9. Based on these data from the latest data cut-off (August 2021), the overall safety profile of tafamidis is consistent with that previously reported in the ATTR-ACT study.

**Impact on health-related quality of life** Clinical documentation for ATTRwt patients:  
EQ-5D-3L at month 30: Least squares (LS) mean difference compared with placebo: [REDACTED]  
EQ-VAS at month 30: LS mean difference compared with placebo: [REDACTED]  
Health economic model: better than comparator

**Type of economic analysis that is submitted** Cost-utility analysis (CUA): a multi-state, Markov model

**Data sources used to model the clinical effects** ATTR-ACT study (3) for placebo arm.  
ATTR-ACT LTE study (4) for tafamidis treatment arm

**Data sources used to model the health-related quality of life (HRQoL)** EQ-5D-3L from the ATTR-ACT study (3). The HRQoL has been mapped to 5L, using Danish population weights.

**Life years gained** [REDACTED]

**QALYs gained** [REDACTED]

**Incremental costs** [REDACTED] based on Pharmacy Purchasing Price (PPP)



Summary	
ICER (DKK/QALY)	██████████
Uncertainty associated with the ICER estimate	██████████ ██████████
Number of eligible patients in Denmark	Prevalence: ██████████ with ATTRwt expected to be initiated in year 1 Incidence: ██████████ with ATTRwt annually
Budget impact (in year 5)	██████████

### 3. The patient population, intervention, choice of comparator(s) and relevant outcomes

#### 3.1 The medical condition

Please see the initial application dated 20 May 2020.

#### 3.2 Patient population

Please see the initial application for a general description of the patient population.

The current application is limited to patients with ATTRwt New York Heart Association (NYHA) class I-III.

No estimates of the prevalence or incidence of ATTRwt in Denmark have been published.

In the DMC assessment from 2022, the expert committee assumed that 275 ATTRwt patients would initiate treatment with tafamidis within the first 2 years after recommendation of tafamidis, i.e., 137,5 patients each year. Thereafter, 50 new patients would initiate treatment each year (5). As this assessment was made based on data from 2021, Pfizer asked the clinical experts, Professor Finn Gustafsson (FG) and Clinical Professor Steen Hvitfeldt Poulsen (SHP), to reassess the expected number of eligible patients to ensure that no major changes have occurred since. Their assessment from January 2024 was that ██████ patients would initiate treatment in year 1, and that ██████ patients would start treatment annually thereafter. This estimate ends with a population



size in year 5, that is very similar to that estimated by the expert committee. The population estimated in Table 1 is based on the updated input from the clinical experts. Please see section 3.4 of the Technical Report for further details.

**Table 1 Estimated number of ATTRwt patients eligible for treatment**

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total after year 5
Number of patients in Denmark who are eligible for treatment in the coming years						
NYHA I/III	■	■	■	■	■	■
Of which: NYHA I/II	■	■	■	■	■	■

### 3.3 Current treatment options

Please see the initial application.

### 3.4 The intervention

Please see the initial application.

#### 3.4.1 The intervention in relation to Danish clinical practice

Please see the initial application.

### 3.5 Choice of comparator(s)

Currently, there are no approved treatment for Danish patients with ATTRwt. Tafamidis will therefore be compared to placebo.

### 3.6 Cost-effectiveness of the comparator(s)

This section is not applicable, as the comparator is placebo.

### 3.7 Relevant efficacy outcomes

#### 3.7.1 Definition of efficacy outcomes included in the application.

Please see the initial application for a description of the relevant endpoints.



In the present application, long-term follow-up for the endpoint overall survival (OS) is included and presented in section 6.1.4. In addition, recent safety data and health-related quality of life (HRQoL) data is presented in section 9 and 10, respectively.

As the current application only concerns patients with ATTRwt treated with tafamidis 80 mg, data is presented for this specific population, whenever possible. However, as published data for this specific subpopulation is not always available, data for a broader study population are presented for some parameters. It is always clearly specified which patient population data is presented for.

**Table 2 Efficacy outcome measures relevant for the application**

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) ATTR-ACT LTE study	At the most recent data cut-off (1 August 2021), when median follow-up was ~60 months.	All-cause mortality is defined as the time from enrollment in ATTR-ACT to death from any cause.	The primary efficacy outcome in the LTE study was all-cause mortality, with heart transplant and implantation of a cardiac mechanical assist device treated as death.  Differential all-cause mortality in the study arms was assessed by Cox proportional hazards model with treatment, genotype (ATTRwt and ATTRm), and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in the model.

\* Time point for data collection used in analysis (follow up time for time-to-event measures)

#### Validity of outcomes

ATTR-CM is a life-threatening disease which leads to a shortened lifespan. Furthermore, OS was a critical endpoint in the initial assessment process and application to the DMC.

## 4. Health economic analysis

For the full details on the health economic modelling, please refer to the Technical Report.





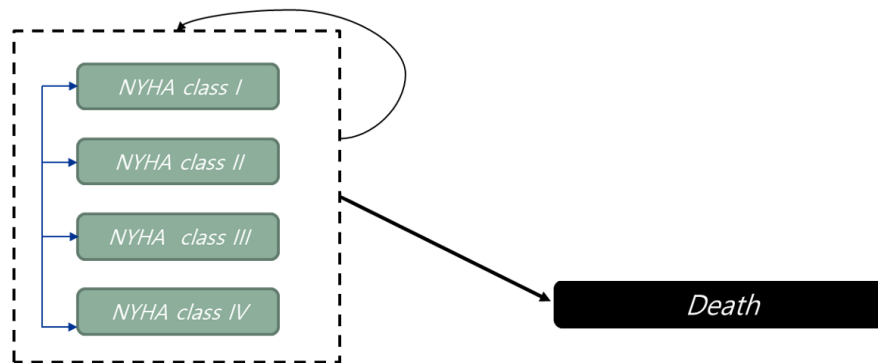
## 4.1 Model structure

As ATTR-CM affects both life expectancy (mortality) and quality of life (morbidity), the model used in this application is a cost-utility analysis (CUA). The model is a multi-state, cohort Markov model developed in Microsoft Excel to capture all costs and outcomes associated with patients receiving tafamidis (intervention) or placebo (comparator).

The model (see Figure 1) tracks ATTR-CM-diagnosed patients according to two main groups of health states: alive and dead. The “alive” state is divided into the 4 NYHA class stages, see Figure 1. The model design allows for alive patients to transition between NYHA class states to examine treatment benefits on disease progression, where disease progression is represented by NYHA classes.

No patients enter the model in NYHA class IV or death health state. Besides these restrictions on the baseline health states, the model is fully flexible regarding the movements between states except for death. Death is an absorbing health state. Please see the Technical Report, section 4.5 for details.

**Figure 1 Model structure**



## 4.2 Model features

**Table 3 Features of the economic model**

Model features	Description	Justification
Patient population	Patients with ATTRwt, NYHA class I-III, treated with tafamidis 80/61 mg or placebo.	In line with the application population.  80 mg tafamidis meglumine has proved bioequivalent to the approved 61 mg tafamidis free acid (6).
Perspective	Limited societal perspective	According to DMC guidelines.
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	30.44 days	An average month.



Model features	Description	Justification
Half-cycle correction	Yes	Standard procedure.
Discount rate	3.5%	The DMC applies a discount rate of 3.5% for all years.
Intervention	Tafamidis 61 mg (Vyndaqel®) once daily	In line with the label.
Comparator(s)	Placebo	There are no other approved therapies for ATTRwt besides tafamidis.
Outcomes	OS	OS is a clinically relevant endpoint and the data formed part of the primary endpoint of the ATTR-ACT LTE study.

## 5. Overview of literature

### 5.1 Literature used for the clinical assessment

For the clinical assessment, data from the ATTR-ACT LTE study is included to provide OS from the latest available follow-up. ATTR-ACT LTE was the long-term extension study of the original ATTR-ACT study described in the original application. The ATTR-ACT study was the pivotal phase III randomized controlled trial (RCT) comparing tafamidis with placebo. No additional RCTs with tafamidis has been performed, and no systematic literature search has therefore been performed.



**Table 4 Relevant literature included in the assessment of efficacy and safety**

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
<p>Full papers:</p> <p>Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. <i>Eur J Heart Fail.</i> 2023 Nov;25(11):2060-2064. (2)</p> <p>Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB, Shah SJ. Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. <i>Circ Heart Fail.</i> 2022 Jan;15(1):e008193. (1)</p>	ATTR-ACT LTE study	NCT02791230	<p>Start: 13/06/16</p> <p>Estimated completion: 16/02/27</p> <p>Data cut-off: 20/03/2020 and 01/08/21 used in Elliott et al., 2022 and Elliott et al., 2023, respectively.</p> <p>Future data cut-offs [REDACTED]</p>	Continuous tafamidis vs. placebo to tafamidis for adult patients with ATTR-CM

## 5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data was obtained from a the ATTR-ACT study which is a RCT comparing tafamidis and placebo for up to 30 months. A literature search was therefore not performed.

However, due to insufficient sample size, NYHA class IV data directly from the study could not be reliably converted between EQ-5D instruments and thus was not used in this analysis. To impute NYHA class IV utilities, utility values from the ATTR-ACT study from the NICE assessment (7) were used instead. Please see section 10.2.1.1.



**Table 5 Relevant literature included for (documentation of) health-related quality of life**

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Not relevant: Data on EQ-5D-3L from the ATTR-ACT study has been reported in (3), yet specific data on ATTRwt patients or according to NYHA class has not been published. Therefore, data on file was used (8).	The HRQoL from the ATTR-ACT study was mapped to EQ-5D-5L and Danish tariffs.	Data on EQ-5D-3L and EQ-VAS is described in section 10.

### 5.3 Literature used for inputs for the health economic model

No literature search has been conducted for inputs for the health economic model. Inputs used and evaluated in the original application were not changed, and no data from the literature has been updated in the current application, therefore no search was conducted.



## 6. Efficacy

### 6.1 Efficacy of tafamidis compared to placebo for patients with ATTR-CM

#### 6.1.1 Relevant studies

Table 6 Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
ATTR-ACT LTE, NCT02791230 (1, 2)	Open label long-term extension study	60 months	Patients having completed ATTR-ACT, NCT01994889	Patients receiving tafamidis (80 or 20 mg tafamidis meglumine) in ATTR-ACT initially continued this dose in the LTE study. Those who had received placebo in ATTR-ACT were randomized 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype. Following a protocol amendment in July 2018, patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg.	None	All-cause mortality (month 60), incidence of treatment emergent adverse events (TEAE) (month 60), cardiovascular (CV)-related mortality (month 60), all-cause hospitalization (month 60), CV-related hospitalization (month 60), Kansas City Cardiomyopathy Questionnaire (KCCQ) (month 60), NYHA classification (month 60), Body Mass Index (BMI)/modified BMI (month 60), cardiac biomarkers (month 60)



### 6.1.2 Comparability of studies

Not applicable, as no studies are compared.

#### 6.1.2.1 Comparability of patients across studies

Not applicable, as patients are not compared across studies.

### 6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Please see previous application and "Medicinrådets vurdering af tafamidis til behandling af transthyretinmedieret amyloidose med kardiomyopati", version 1, dated 23 September 2020, for the Danish Medicines Council's assessment of the comparability.

### 6.1.4 Efficacy – results per ATTR-ACT LTE

As agreed with the Secretariat, the current application for reassessment only includes long-term follow-up data on all-cause mortality from the ATTR-ACT LTE study, which was not available at the time of the original application.

Patients with wild-type and hereditary ATTR-CM, who completed the ATTR-ACT study, could enroll in an LTE study (NCT02791230) to receive up to an additional 60 months of tafamidis treatment. Patients receiving tafamidis (80 or 20 mg tafamidis meglumine) in the ATTR-ACT study initially continued this dose in the ATTR-ACT LTE study. Patients who had received placebo in ATTR-ACT were randomized 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype. Following a protocol amendment in July 2018, patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg (6). For convenience, 80 mg tafamidis meglumine is designated as 80 mg tafamidis in the following. A dose reduction could be requested if patients experienced adverse events, and patients receiving tafamidis 80 mg could have their dose reduced to 20 mg.

Due to the design of ATTR-ACT study, data on ATTRwt is not available for all parameters required by the Medicine Council. The table below shows the specific study populations used for each parameter and the time of data cut-off are specified.

**Table 7 Overview of the time of data cuts used for the different patient populations**

Data category	Data source
OS	<b>ATTR-CM:</b> ATTR-ACT LTE, data cut March 20, 2020 (1)
	<b>ATTRwt:</b> Clinical information: ATTR-ACT LTE, data cut March 20, 2020 (1) Health Economic model: placebo: Placebo: ATTR-ACT, data on file (8). Health Economic model: tafamidis 80 mg: ATTR-ACT LTE, data cut [REDACTED]. Data on file (4).



Data category	Data source
	<b>ATTR-CM, NYHA I/II at baseline:</b> ATTR-ACT LTE, data cut August 1, 2021 (2, 4)
Safety	Clinical information: ATTR-ACT LTE, data cut August 1, 2021 (2) Health Economic model: ATTR-ACT, data on file (8)
Discontinuation	ATTR-ACT LTE, data cut [REDACTED] (4)
HRQoL	ATTR-ACT, data on file (4)
Health care resource utilization	ATTR-ACT, data on file (8)

## All-cause mortality

### All-cause mortality for ATTR-CM (ATTRwt and ATTRm) patients

All-cause mortality was the primary efficacy outcome in the ATTR-ACT LTE study. The most recent data based on the entire study population (i.e., ATTRwt and ATTRm) is derived from the data cut-off of March 20, 2020 which has been published by Elliott et al. 2022 (1). Here, patients who were continuously treated with tafamidis 80/61 mg were compared to patients treated with placebo in ATTR-ACT and transferred to tafamidis in the ATTR-ACT LTE study. For both groups, baseline for survival analyses was the time of enrollment in ATTR-ACT (1).

Baseline demographic and clinical characteristics of patients included in ATTR-ACT have been published previously (9). A total of 110 patients treated with tafamidis 80 mg continued in the ATTR-ACT LTE study on the same dose. A total of 82 placebo-treated patients continued in the ATTR-ACT LTE study, 54 of whom were randomized to tafamidis 80 mg and 28 to tafamidis 20 mg (1). After the protocol amendment, all patients receiving treatment with tafamidis were switched to receive the approved dose of 61 mg tafamidis. Patients in the tafamidis 20 mg arm in ATTR-ACT were not included in the statistical analysis as this dose is not approved for the treatment of patients with ATTR-CM.

At the data cut-off in March 2020, the median follow-up time was 58.5 months in the continuous tafamidis group (n=176) and 57.1 months in the placebo to tafamidis group (n=177) (1).

Results for all patients (ATTRwt and ATTRm) receiving tafamidis 80/61 mg are presented in Table 8. Although the median survival was 67.0 (47.0–non-estimable) months in the continuous tafamidis group, the high degree of censoring before this time point suggests that the estimate is subject to change. Based on post hoc analyses using Cox proportional hazards model, there was no significant interaction of treatment with genotype (p=0.58) (1).



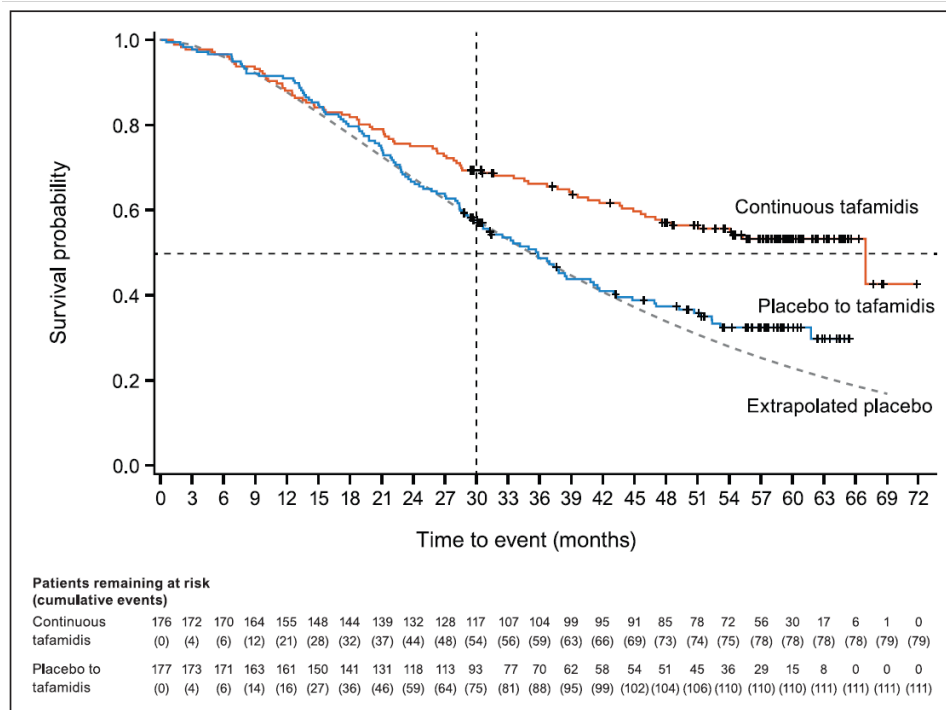
**Table 8 All-cause mortality with tafamidis for all patients (ATTRwt and ATTRm) at interim analysis of the ATTR-ACT LTE study**

	Continuous tafamidis 80/61 mg (ATTR-ACT study: <i>n</i> =176 ATTR-ACT LTE study: <i>n</i> =110)	Placebo to tafamidis 80/61 mg (ATTR-ACT study: <i>n</i> =177 ATTR-ACT LTE study: <i>n</i> =82)
All-cause mortality, <i>n</i> (%)	79 (44.9)	111 (62.7)
Deaths	70 (39.8)	105 (59.3)
Heart transplant	7 (4.0)	6 (3.4)
Implantation of a cardiac mechanical assist device	2 (1.1)	0
Kaplan–Meier estimates of time to event (death), median (95% CI), months	67.0 (47.0–N/E) <sup>1</sup>	35.8 (29.7–41.1)
Kaplan–Meier preliminary estimates of 5-years survival, %	53.2	32.4
Tafamidis vs placebo HR (95% CI), <i>P</i> value	0.59 (0.44–0.79), <i>p</i> <0.001	

<sup>1</sup> The high degree of censoring before this time point suggests that the estimate is subject to change. Median follow-up was 58.5 months with continuous tafamidis and 57.1 months with placebo to tafamidis (1). HR from Cox proportional hazards model with treatment, genotype (ATTRwt and ATTRm), and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in model. Data cut-off: March 20, 2020. ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; LTE, long-term extension; N/E, nonestimable; NYHA, New York Heart Association.

In Figure 2, the survival curves for the two treatment arms (continuous tafamidis and placebo to tafamidis) are depicted (1). In this figure, the extrapolated placebo curve (dotted line) is a model-based extrapolation of survival in placebo-treated patients in ATTR-ACT beyond 30 months (10).





**Figure 2 Kaplan–Meier plot of observed time to all-cause mortality in the ATTR-ACT and ATTR-ACT LTE studies and compared with model-based extrapolation of time to all-cause mortality with placebo**

Time to all-cause mortality (with heart transplant and implantation of a cardiac mechanical assist device treated as death) shown for all patients treated with tafamidis 80 mg in ATTR-ACT continuing with tafamidis 80 mg, then tafamidis free acid 61 mg in the ATTR-ACT LTE study (continuous tafamidis) compared with patients treated with placebo in ATTR-ACT continuing with tafamidis (20, 80, or 61 mg) in the ATTR-ACT LTE study (placebo to tafamidis) (1). The extrapolated placebo curve (dotted line) is a model-based extrapolation of survival in placebo-treated patients in ATTR-ACT beyond 30 months (10). Data cut-off: March 20, 2020.

### All-cause mortality for ATTRwt patients

All-cause mortality for ATTRwt patients based on the data cut-off of March 20, 2020 was also published in Elliott et al. 2022 (1).

In patients with continuous tafamidis treatment, there was a 39% reduction in the risk of all-cause mortality in patients with ATTRwt (HR, 0.61 [95% CI, 0.43–0.87];  $p=0.006$ ) compared with the placebo to tafamidis group (Table 9). The preliminary 5-year survival rate in patients with ATTRwt was 57.8% with continuous tafamidis treatment and 36.3% in the placebo to tafamidis group (1).

The survival curves for the two treatment arms (continuous tafamidis and placebo to tafamidis) for ATTRwt patients are depicted in Figure 3.



**Table 9 All-cause mortality with tafamidis in ATTRwt patients at interim analysis of the ATTR-ACT LTE study**

	Continuous tafamidis 80/61 mg ATTR-ACT: <i>n</i> =134	Placebo to tafamidis 80/61 mg ATTR-ACT: <i>n</i> =134
All-cause mortality, <i>n</i> (%)	54 (40.3)	80 (59.7)
Deaths	51 (38.1)	75 (56.0)
Heart transplant	3 (2.2)	5 (3.7)
Implantation of a cardiac mechanical assist device	0	0
<b>Kaplan–Meier estimates of time to event (death), median (95% CI), months</b>	67.0 (54.4–N/E) <sup>1</sup>	38.6 (34.1–47.1)
<b>Kaplan–Meier preliminary estimates of 5-years survival, %</b>	57.8	36.3
<b>Tafamidis vs placebo HR (95% CI), <i>P</i> value</b>	0.61 (0.43–0.87), 0.006	

<sup>1</sup> The high degree of censoring before this time point suggests that the estimate is subject to change. Median follow-up in ATTRwt was 58.3 months with continuous tafamidis and 57.5 months with placebo to tafamidis. HR from Cox proportional hazards model with treatment and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in model. Data cut-off: March 20, 2020 (1). ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTRwt, wild-type transthyretin amyloidosis; LTE, long-term extension; N/E, nonestimable.



**Figure 3** [REDACTED]

**All-cause mortality for ATTR-CM (ATTRwt and ATTRm) patients according to NYHA class**

A post-hoc analysis including data on all-cause mortality from the latest interim data cut-off (1 August 2021) has assessed all-cause mortality according to NYHA class (2). In this analysis, two groups were compared: (1) patients who received continuous tafamidis (tafamidis meglumine 80 mg in ATTR-ACT and then tafamidis free acid 61 mg in the ATTR-ACT LTE study); and (2) those who received placebo in ATTR-ACT and then tafamidis in the ATTR-ACT LTE study (termed the placebo to tafamidis group). Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT were not included in this analysis (2).

The median follow-up time from ATTR-ACT baseline to the ATTR-ACT LTE study interim analysis was 61 months for patients in the continuous tafamidis group and 59 months for those in the placebo to tafamidis group (2).

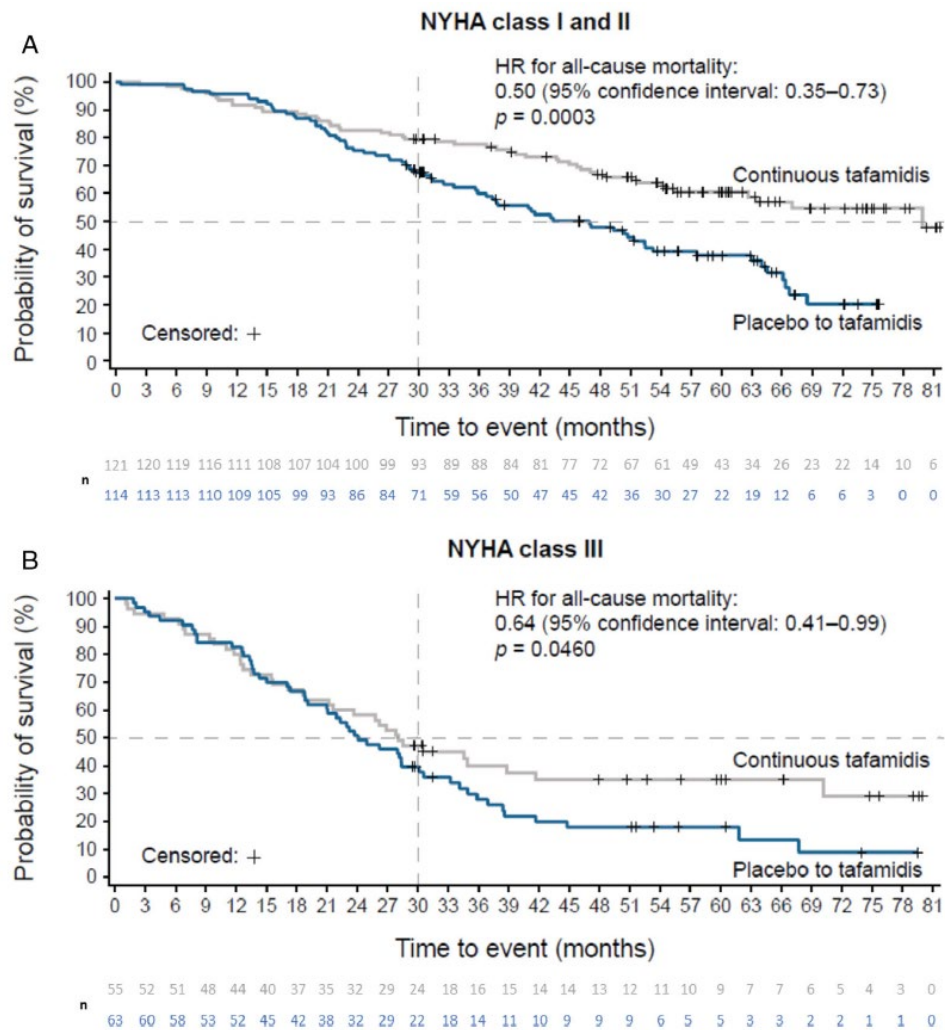
All-cause mortality was assessed by NYHA class (I/II or III) using a Cox proportional hazards model with treatment and genotype included in the model. Heart transplantation or implantation of a mechanical ventricular assist device were considered equivalent to death.



All-cause mortality for NYHA class I/II patients was 41% in the continuous tafamidis group and 61% in the placebo to tafamidis group, with a HR favorable towards continuous tafamidis treatment (HR 0.50; 95% CI: 0.35–0.73;  $p=0.0003$ ).

All-cause mortality in NYHA class III patients was 64% in the continuous tafamidis group and 81% in the placebo to tafamidis group with a HR: 0.64 (95% CI: 0.41–0.99;  $p=0.0460$ ) (2).

A Kaplan–Meier curve of observed all-cause mortality over time is presented in Figure 4 for patients in NYHA class I/II (A) and III (B), and additional information on all-cause mortality is provided in Table 10.



**Figure 4 Kaplan–Meier curve of observed all-cause mortality in the ATTR-ACT study and its LTE by baseline NYHA class**

HR provided for all patients (ATTRwt and ATTRm patients pooled) continuously treated with tafamidis meglumine 80 mg/tafamidis free acid 61 mg versus placebo then tafamidis (2). HR: Hazard ratio.



**Table 10 All-cause mortality with tafamidis in ATTRwt and ATTRm patients (pooled) by baseline NYHA class at August 2021 interim analysis of the ATTR-ACT LTE study**

	NYHA class I/II		NYHA class III	
	Continuous tafamidis (n=121)	Placebo to tafamidis (n=114)	Continuous tafamidis (n=55)	Placebo to tafamidis (n=63)
<b>Follow-up<sup>a</sup>, months, median (95% CI)</b>	61 (60–66)	60 (56–65)	60 (48–75)	56 (51–74)
<b>All-cause mortality after treatment initiation</b>				
<b>n (%)</b>	49 (40.5)	70 (61.4)	35 (63.6)	51 (81.0)
<b>due to:</b>				
Death	42 (34.7)	64 (56.1)	33 (60.0)	51 (81.0)
Heart transplant	6 (5.0)	6 (5.3)	1 (1.8)	0
Mechanical ventricular assist device implantation	1 (0.8)	0	1 (1.8)	0

Patients continuously treated with tafamidis meglumine 80 mg/free acid 61 mg, or placebo then tafamidis (2).  
<sup>a</sup>Median follow-up duration from Kaplan–Meier method. Data is based on the interim data cut-off of 1 August 2021. CI, confidence interval; LTE, long-term extension; NYHA, New York Heart Association.



## 7. Comparative analyses of efficacy

This section is not applicable, as ATTR-ACT is a head-to-head study comparing tafamidis with placebo, and the LTE study is a continuation of the ATTR-ACT study. Results from the comparative analysis are provided in Table 11.



**Table 11 Results from the comparative analysis of continuous tafamidis 80/61 mg vs. placebo to tafamidis for patients with ATTR-CM**

Population	Outcome measure	Continuous tafamidis 80/61 mg	Placebo to tafamidis 80/61 mg	Result
ATTR-CM (ATTRwt and ATTRm) (1)	<i>n</i>	176	177	-
	OS	Median: 67.0 months (95 % CI: 47.0–N/E)	Median: 35.8 months (95 % CI: 29.7–41.1)	HR: 0.59 (95% CI: 0.44–0.79)
	Preliminary 5-year survival rate, %	53.2	32.4	20.8 <sup>#</sup>
ATTRwt (1)	<i>n</i>	134	134	-
	OS	67.0 months (95% CI: 54.4–N/E)	38.6 months (95 % CI: 34.1–47.1)	HR: 0.61 (95% CI: 0.43–0.87)
	Preliminary 5-year survival rate, %	57.8	36.3	21.5 <sup>#</sup>
NYHA class I/II (ATTRwt and ATTRm) (2)	<i>n</i>	121	114	-
	All-cause mortality, %	41	61	HR 0.50 (95% CI: 0.35–0.73)
NYHA class III (ATTRwt and ATTRm) (2)	<i>n</i>	55	63	-
	All-cause mortality, %	64	81	HR: 0.64 (95% CI: 0.41–0.99)

<sup>#</sup>Values have not been published and have been calculated by us for the current application

## 8. Modelling of efficacy in the health economic analysis

### 8.1 Presentation of efficacy data from the clinical documentation used in the model

In the model, treatment efficacy for tafamidis or placebo is captured through health state occupancy, survival estimates and incidence of hospitalizations. All patients start in the model as alive in one of the NYHA class health states.



The general approach is described here, but please see the Technical Report for full details, including information on the changes made compared to the original application.

### 8.1.1 Extrapolation of efficacy data

The proportion of patients who dies in each cycle is informed by the mortality data from the Kaplan-Meier (KM) curve from the ATTR-ACT study (11), including the ATTR-ACT LTE study (4), see Figure 5.

The model corrects study OS for background general population mortality, as the OS data used in the model is adjusted using the maximum hazard of dying for background mortality vs. from the trial at each cycle, such that at any age, the risk of dying cannot be lower than that for the general population.

The model does not determine health state-specific OS, as the small sample sizes in the NYHA I and NYHA IV classes would limit the ability to generate robust NYHA class-specific extrapolations of survival. Instead, the treatment-specific OS KM curve used in the model base case is based on the KM-curve for the ATTRwt patients pooled across all NYHA classes.

Data up to 30 months of follow-up were available from the ATTR-ACT study for both treatment arms. For the tafamidis treatment arm however, data up to 84 months of follow-up were also available from a combined analysis of ATTR-ACT and the LTE study (cut-off date: 1 August, 2021). Please see the Technical Report for further details.

#### 8.1.1.1 Extrapolation of survival

**Table 12 Summary of assumptions associated with extrapolation of survival**

Method/approach	Description/assumption
<b>Data input</b>	Placebo: ATTR-ACT (8)
	Tafamidis: ATTR-ACT & LTE, data cut of [REDACTED] (4)
<b>Model</b>	The model uses full parametrization
<b>Assumption of proportional hazards between intervention and comparator</b>	The proportional hazards assumption is violated.
	Please see the Technical Report for details.
<b>Function with best AIC fit</b>	Intervention: LogNormal function Placebo: Gompertz function
<b>Function with best BIC fit</b>	Intervention: Exponential function Placebo: Gompertz function
<b>Function with best visual fit</b>	Intervention: Weibull and Gamma both fit. Placebo: Weibull, Gompertz, and Generalized Gamma all fit



<b>Method/approach</b>	<b>Description/assumption</b>
<b>Function with best fit according to evaluation of smoothed hazard assumptions</b>	Not relevant, please see the discussion of evidence in the Technical report, section 4.6.1.
<b>Validation of selected extrapolated curves (external evidence)</b>	Please see the discussion of evidence in the Technical report, section 4.6.1.
<b>Function with the best fit according to external evidence</b>	Please see the discussion of evidence in the Technical report, section 4.6.1.
<b>Selected parametric function in base case analysis</b>	Intervention: Gamma function Placebo: Gompertz function
<b>Adjustment of background mortality with data from Statistics Denmark</b>	Yes
<b>Adjustment for treatment switching/cross-over</b>	No
<b>Assumptions of waning effect</b>	No
<b>Assumptions of cure point</b>	No





**Figure 5** [REDACTED]

Source: CUA, Data on file.

### 8.1.2 Calculation of transition probabilities

Living patients could transition between NYHA classes through transition probabilities:

For the first 30 months of the model time horizon, the number of alive patients in a given NYHA class in cycle (n) were informed by the observed longitudinal data of the total intent-to-treat (ITT) population at cycle n in the ATTR-ACT trial.

After 30 months in the model, the number of patients in each NYHA class in each cycle was instead determined in a two-step process: Step 1 removed dead patients in cycle n by NYHA class. Step 2 transitioned alive patients to a NYHA class in cycle n+1.

Instead of assuming that there is an equal risk of death across NYHA classes, the probability of mortality by NYHA class from the ATTR-ACT, 30-month study (for the placebo arm) and from the LTE study (for the tafamidis arm) was used, see Table 13.



**Table 13 Distribution of mortality by NYHA class for patients with ATTRwt from the ATTR-ACT study and its LTE**

NYHA class at time of death	Tafamidis [REDACTED]	Placebo (30-months follow-up)
NYHA I	[REDACTED]	[REDACTED]
NYHA II	[REDACTED]	[REDACTED]
NYHA III	[REDACTED]	[REDACTED]
NYHA IV	[REDACTED]	[REDACTED]

Source: The ATTR-ACT study and ATTR-ACT LTE study (12)

A transition probabilities matrix was used to estimate the number of patients that would move to another NYHA class in each cycle after month 30 (Table 14).

For the placebo arm, these transition probabilities were based on transitions in the ATTR-ACT study between months 24 and 30. For the tafamidis arm, these transition probabilities were based on transitions from the longer-term data between months 30 and 72. Note that for the NYHA class IV to NYHA class IV transition, the probability was assumed to be 100%.

To calculate the transition probabilities, [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED], and then converted to a monthly probability. Patients who did not transition to another NYHA class and did not die remained in their starting NYHA class. The matrix generally allows for free transition between any NYHA class stage. Thus, patients could progress or regress by more than one class within a cycle. For details on the calculations or the assumptions behind the calculations, please see the Technical Report, section 4.6.2.

**Table 14 Transition probabilities for ATTRwt from the ATTR-ACT study and LTE study**

		To NYHA I	To NYHA II	To NYHA III	To NYHA IV
<b>Tafamidis</b> (Months 30-72)	From NYHA I	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	From NYHA II	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	From NYHA III	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	From NYHA IV	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Placebo</b> (Months 24-30)	From NYHA I	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	From NYHA II	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	From NYHA III	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



From NYHA IV



Source: Model sheet: Transition Probabilities. Please note that rows may not sum up to 1.0 due to rounding rules.

Table with 25 rows of redacted data (XXXXXX).

Figure 6 [Redacted]

Source: Model sheet: Results.



**Figure 7** [Redacted]

Source: Model sheet: Results.

## 8.2 Presentation of efficacy data from [additional documentation]

Not applicable, as all efficacy data came from the pivotal study, and/or the LTE study.

## 8.3 Modelling effects of subsequent treatments

Not applicable, as subsequent treatment is not included in the model.

## 8.4 Other assumptions regarding efficacy in the model

Not relevant.

## 8.5 Overview of modelled average treatment length and time in model health state

Table 15 shows the estimated time on treatment in the model for ATTRwt patients. Please see the Technical Report for further information.



**Table 15 Estimates in the model for the ATTRwt population**

	Modelled average Survival (see “Results (DMC)” in model)	Modelled median Survival (reference in Excel)	Observed median from relevant study
Tafamidis	██████	██████	Data is not finally assessed. <sup>2</sup>
Placebo	██████	██████	38.6 months for patients on placebo and then switched to tafamidis <sup>1</sup>

<sup>1</sup> Please see Appendix B about Efficacy results per study ATTR-ACT LT and Elliott et al 2022 (1). ██████████  
 ██████████

Table 16 shows the modelled average treatment length and time in model health states. These are derived in accordance with the modelling described regarding mortality and transition between health states.

**Table 16 Overview of modelled average treatment length (months) and time in model health state, undiscounted and not adjusted for half cycle correction**

Treatment	Treatment length	NYHA I	NYHA II	NYHA III	NYHA IV
Tafamidis	████	████	████	████	████
Placebo	████	████	████	████	████

Source: Model sheet: Results – Base Case.

## 9. Safety

### 9.1 Safety data from the clinical documentation

Adverse events in patients receiving continuous tafamidis in the ATTR-ACT LTE study, as of the latest data-cut (1 August 2021) have been published (2) and are presented in Table 17. The safety population was defined as all patients treated with tafamidis 80 mg in the ATTR-ACT study who enrolled and continued to receive tafamidis in the ATTR-ACT LTE study. At the time of the data cut-off, the median follow-up was approximately 60 months.

Overall, the safety profile of tafamidis based on data from the ATTR-ACT LTE study was consistent with that previously reported in the ATTR-ACT study (2).



**Table 17 Adverse events reported in patients receiving continuous tafamidis in the ATTR-ACT LTE study**

Patients, <i>n</i> (%)	Continuous tafamidis <i>n</i> = 110
<b>Any adverse effect in the ATTR-ACT LTE study</b>	<b>108 (98.2)</b>
<b>Cardiac disorders</b>	<b>79 (71.8)</b>
Cardiac failure	28 (25.5)
Atrial fibrillation	21 (19.1)
Ventricular tachycardia	13 (11.8)
Cardiac failure (acute)	11 (10.0)
Cardiac failure (congestive)	9 (8.2)
Pericardial effusion	7 (6.4)
<b>Infections and infestations</b>	<b>64 (58.2)</b>
Cellulitis	17 (15.5)
Urinary tract infection	14 (12.7)
Pneumonia	13 (11.8)
Upper respiratory tract infection	8 (7.3)
Bronchitis	7 (6.4)
Nasopharyngitis	7 (6.4)
<b>Injury, poisoning, and procedural complications</b>	<b>57 (51.8)</b>
Fall	31 (28.2)
Skin abrasion	9 (8.2)
Contusion	7 (6.4)
Skin laceration	7 (6.4)
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>55 (50.0)</b>
Dyspnoea	20 (18.2)
Cough	18 (16.4)
Pleural effusion	18 (16.4)
Epistaxis	9 (8.2)
<b>General disorders and administration site conditions</b>	<b>54 (49.1)</b>
Oedema (peripheral)	16 (14.5)
Fatigue	12 (10.9)
Asthenia	9 (8.2)
Chest pain	8 (7.3)
<b>Gastrointestinal disorders</b>	<b>50 (45.5)</b>
Constipation	11 (10.0)
Nausea	11 (10.0)
Ascites	9 (8.2)
Diarrhoea	8 (7.3)



Patients, <i>n</i> (%)	Continuous tafamidis <i>n</i> = 110
Dysphagia	7 (6.4)
<b>Nervous system disorders</b>	<b>51 (46.4)</b>
Dizziness	15 (13.6)
Balance disorder	9 (8.2)
<b>Musculoskeletal and connective tissue disorders</b>	<b>49 (44.5)</b>
Arthralgia	21 (19.1)
Pain in extremity	12 (10.9)
Back pain	9 (8.2)
Osteoarthritis	8 (7.3)
Muscle spasms	7 (6.4)
Muscular weakness	7 (6.4)
<b>Metabolism and nutrition disorders</b>	<b>43 (39.1)</b>
Hypokalaemia	12 (10.9)
Gout	10 (9.1)
Hyponatraemia	8 (7.3)
Decreased appetite	7 (6.4)
<b>Skin and subcutaneous tissue disorders</b>	<b>42 (38.2)</b>
Pruritus	11 (10.0)
Skin ulcer	8 (7.3)
<b>Renal and urinary disorders</b>	<b>35 (31.8)</b>
Acute kidney injury	18 (16.4)
Renal failure	8 (7.3)

Patients continuously treated with tafamidis meglumine 80 mg or free acid 61 mg. Includes system organ classes where  $\geq 30\%$  of patients in the study had an adverse event, and within these, MedDRA Preferred Terms in  $\geq 6\%$  of patients. Adverse events reported up to 28 days after the patient's last dose of tafamidis. Data from the interim ATTR-ACT LTE study analysis dated 1 August 2021 (2). Events coded per MedDRA v24.0. LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities.

The adverse events (AEs) and frequency of AEs included in the model are unchanged compared to the original reimbursement application and thus reflects the data available at the 30-month cut-off. In the health economic model, the numbers may differ from the safety section above, due to that only AEs related to tafamidis meglumine 80 mg (bioequivalent to tafamidis free acid 61 mg) are included (8). Please see Table 18 below.



**Table 18 Adverse events used in the health economic model**

Adverse events	Intervention	Comparator	Source	Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		
Diarrhea	████	████	ATTR-ACT	See original application
Urinary tract infection (UTI)	████	████	ATTR-ACT	See original application
Nausea	████	████	ATTR-ACT	See original application

## 9.2 Safety data from external literature applied in the health economic model

This section is not relevant since safety data is not derived from external literature.

# 10. Documentation of health-related quality of life (HRQoL)

In the ATTR-ACT study, several measures of HRQoL were included (11), however, in line with DMC recommendation, only EQ-5D is presented here and is included in the health economic model.

Please note that all data in this section is presented for the model population, i.e., patients with ATTRwt only. Furthermore, for patients in the active treatment arm, all data is for patients treated with tafamidis 80 mg.

**Table 19 Overview of included HRQoL instruments**

Measuring instrument	Source	Utilization
EQ-5D-3L	ATTR-ACT	This is the HRQoL instrument preferred by the DMC.





## 10.1 Presentation of the health-related quality of life

### 10.1.1 Study design and measuring instrument EQ-5D-3L

HRQoL, assessed as the change from baseline at each time point in EuroQoL-5 Dimensions 3-Levels (EQ-5D-3L) Index Score and visual analog scale (VAS) scores, was included as one of the exploratory end points in the randomized, controlled ATTR-ACT study.

Transthyretin amyloidosis is associated with a decreased HRQoL (13, 14) and the EQ-5D-3L questionnaire was chosen as measuring instrument, as this is a generic and validated instrument which is used in many different patient populations and countries for the measurement of HRQoL.

### 10.1.2 Data collection

The EQ-5D-3L questionnaire is a patient-completed health status instrument consisting of 2 parts. In the first, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain, or discomfort, and anxiety or depression), with each dimension having 3 levels of function (1 = no problem, 2 = some problem, and 3 = extreme problem). These scores are used to calculate a single EQ-5D-3L Index Score using country-specific tariffs. In the second, patients rate their current health state on the EQ-VAS, with end points labeled “best imaginable health state” (score of 100) and “worst imaginable health state” (score of 0).

Patients completed the HRQoL assessments, including EQ-5D-3L and EQ-VAS, at the baseline visit and at subsequent visits (months 6, 12, 18, 24, and 30, or at study discontinuation) (3). [REDACTED]

Data in Table 20 shows the pattern of missing data and completion of EQ-3D-3L for the ATTRwt population receiving 80 mg tafamidis.

Data on EQ-5D was evaluated at each time point post-baseline using a mixed model repeated measures (MMRM) ANCOVA with center and patient within center as random effects; treatment, visit, genotype (ATTRm and ATTRwt), and visit by treatment interaction as fixed effects; and baseline score as covariate (6).

There was no imputation of missing values, and it has not been possible to gain any data on characteristics of patients with missing data.



**Table 20 Pattern of missing EQ-5D-3L data and completion for each time point for ATTRwt patients receiving tafamidis 80 mg**

Time point	HRQoL population	Missing	Expected to complete	Completion
	N	N (%)	N	N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	████	████	████	████
6 months	████	████	████	████
12 months	████	████	████	████
18 months	████	████	████	████
24 months	████	████	████	████
30 months	████	████	████	████

Source: Data from ATTR-ACT, data on file (8).

### 10.1.3 HRQoL results

The statistical analyses were carried out on the intent-to-treat (ITT) population, which included all patients who were enrolled, received at least 1 dose of tafamidis or placebo, and had at least 1 after-baseline efficacy evaluation. There was no imputation of missing values.

Table 21 and Table 22 show the summary statistics for the EQ-5D-3L and EQ-VAS, respectively, using UK utility weights.

**Table 21 HRQoL EQ-5D-3L summary statistics for ATTRwt patients receiving tafamidis 80 mg**

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	LS mean difference (95% CI) p-value
Baseline	████	██████████	████	██████████	██████████
6 months	████	██████████	████	██████████	██████████████████
12 months	████	██████████	████	██████████	██████████████████



	Intervention		Comparator		Intervention vs. comparator
18 months	█	█	█	█	█
24 months	█	█	█	█	█
30 months	█	█	█	█	█

Source: Data from ATTR-ACT, data on file (8). Only patients receiving 80 mg tafamidis or placebo are included. L.S = Least Squares. L.S. means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, and visit by treatment interaction, as fixed effects and Baseline score as covariate.

**Table 22 HRQoL EQ-VAS summary statistics for ATTRwt patients**

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	LS mean difference (95% CI) p-value
Baseline	█	█	█	█	█
6 months	█	█	█	█	█
12 months	█	█	█	█	█
18 months	█	█	█	█	█
24 months	█	█	█	█	█
30 months	█	█	█	█	█

Data from ATTR-ACT, data on file (8). Only patients receiving 80 mg tafamidis or placebo are included. L.S = Least Squares. L.S. means are from an ANCOVA (MMRM) model with an unstructured covariance matrix; center and subject within center as random effects; treatment, visit, and visit by treatment interaction, as fixed effects and Baseline score as covariate.

In Figure 8 and Figure 9, the mean change from baseline in EQ-5D-3L index scores and EQ-VAS, respectively, is depicted. Please note that in these figures, the active arm includes patients receiving 80 mg tafamidis only, since this is the dose approved for the treatment of ATTR-CM.



Figure 8 [Redacted]





Figure 9 [REDACTED]

[REDACTED]

## 10.2 Health state utility values (HSUVs) used in the health economic model

### 10.2.1 HSUV calculation

[REDACTED]

The ATTR-ACT study measured HRQoL using KCCQ and EQ-5D-3L. These values were produced through a post-hoc analysis of utility data in the ATTR-ACT study by NYHA class and by treatment regardless of assessment time point (3).



### 10.2.1.1 Mapping

According to DMC guidelines, EQ-5D-5L is strongly preferred over EQ-5D-3L (15). Thus, the EQ-5D-3L data was first converted to EQ-5D-5L data using validated methods from van Hout et al (16). Next step was to convert the values to Danish utility values using weights from Jensen et al (17). This Danish study included a nationally representative sample based on age, gender, education, and region – and interviews were conducted using the EQ-VT 2.1. Respondents valued states based on composite time trade-off (cTTO) and discrete-choice experiments (DCE). A heteroscedastic censored hybrid model combining both the cTTO and DCE data was selected by the authors as the best fitting model, and the version with regular dummies was used to generate HSUVs based on cross-walked EQ-5D-3L to EQ-5D-5L data.

[REDACTED]

[REDACTED]. Results have then been age-adjusted according to DMC guidelines.

Please see the Technical Report Appendix 5 for full details on mapping etc.

### 10.2.2 Disutility calculation

No disutilities associated with adverse events or hospitalizations were applied, as it was assumed such disutility is already captured in the trial-based EQ-5D data.

### 10.2.3 HSUV results

Utilities were generated from EQ-5D-3L data which was translated into EQ-5D-5L data and weighted using Danish utility preference weights.

**Table 23 Overview of health state utility values for ATTRwt**

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
NYHA I – tafamidis 80 mg	[REDACTED]	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA II – tafamidis 80 mg	[REDACTED]	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population



	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NYHA III – tafamidis 80 mg	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA IV – tafamidis 80 mg	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA I – placebo	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA II – placebo	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA III – placebo	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population
NYHA IV - placebo	■	EQ-5D-5L	DK	Estimate based on all ATTR-ACT EQ-5D-3L data for the population

Source: Calculation, see Technical report Appendix 5.

### 10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable, as no other trials are included.

## 11. Resource use and associated costs

### 11.1 Medicine costs - intervention and comparator

Table 24 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Tafamidis	61 mg	■	Once daily	No
Placebo	-	Not relevant	Not relevant	Not relevant



## 11.2 Medicine costs – co-administration

Not applicable.

## 11.3 Administration costs

Tafamidis is taken orally, and patients can administer the medication by themselves. Therefore, no costs are associated with the administration of tafamidis.

## 11.4 Disease management costs

In the current application, costs have been updated to 2023 tariff. No changes have been made as to assumptions or other input in this section. Please see the Technical Report for a full account of costs and assumptions.

Patients are monitored regularly at the hospital. Table 25 presents the assumptions regarding the frequency and cost of follow-up outpatients contacts. The clinical expert SHP has provided estimates by NYHA class.

The unit cost associated with an outpatient contact at the outpatient clinic is DRG rate '05PR04: Extended Cardiac investigation'.

Patients are also seen regularly by their general practitioner (GP) (SHP input). Such a consultation usually includes International Normalized Ratio (INR) testing, measurement of blood pressure and blood tests, and examines patients' disease progression.

Based on input from SHP, Table 25 also presents the estimates of the frequency of visits to the GP in each of the 4 NYHA classes. The unit cost is based on the fee for service payments of GPs in Denmark (18). The cost is set to DKK 282.27 per visit made up of a standard consultation (service code: 0101, DKK 153.61) plus an added fee for service payment of an INR test (service code: 7126, DKK 128.66).

**Table 25 Disease management costs used in the model**

Activity	Frequency (contacts/yr)	Unit cost [DKK]	DRG code	Reference
<b>Outpatient monitoring at hospital</b>				
NYHA I	■	1,975	05PR04	DRG 2023
NYHA II	■	1,975	05PR04	DRG 2023
NYHA III	■	1,975	05PR04	DRG 2023
NYHA IV	■	1,975	05PR04	DRG 2023
<b>Monitoring in primary care</b>				





Activity	Frequency (contacts/yr)	Unit cost [DKK]	DRG code	Reference
NYHA I	█	282.27	0101 + 7126	DMC unit costs
NYHA II	█	282.27	0101 + 7126	DMC unit costs
NYHA III	█	282.27	0101 + 7126	DMC unit costs
NYHA IV	█	282.27	0101 + 7126	DMC unit costs
<b>Average inpatients hospitalization events</b>				
CV-related event	█	█	█	See Technical Report, section 4.7.3
All-cause hospitalization	█	41,804	04MA13	DRG 2023, See Technical Report, section 4.7.3

Due to the progression of the disease, patients also experience frequent hospitalizations. In every model cycle, patients will incur a cost associated with a CV-related or all-cause hospitalization. These costs are calculated based on the unit costs per inpatient hospitalization and the frequency of inpatient hospitalizations. The methods for this are described further in the Technical Report.

For the calculation of all hospitalizations, the clinical experts SHP and FG have explained to Pfizer that there are no published references regarding the unit costs of non-CV-related inpatient hospitalization. The best assumption according to SHP and FG is to use the DRG rate of an inpatient hospitalization with pneumonia (DRG: 04MA13, DKK 41,804 in 2023 prices) since pneumonia was observed as one of the most frequent non-CV related causes of hospitalization in the relevant population (19).

There is currently no data on the healthcare utilization of Danish patients with ATTRwt after diagnosis. To align the assumptions of the base case analysis with the characteristics of the Danish patient population, estimates from the Medical Advisory Board 2019 were relied on (see the Technical Report for details).

Since tafamidis is not yet used as a standard of care for patients with ATTRwt, this knowledge applies to the placebo group. For the placebo group, the number of CV related hospitalizations was assumed to be █ per year, and that off all-cause hospitalizations to be █ per year.

█
█
█
█



Finally, frequencies were converted to per cycle probabilities and applied to all patients who were alive in each cycle over the time horizon, (see the Technical Report Appendix 4).

## 11.5 Costs associated with management of adverse events

Since AEs are most likely to occur with treatment initiation, a one-time total cost for AEs is applied during the first cycle. Please see the Technical Report, section 4.7.2, for details.

**Table 26 Cost associated with management of adverse events**

	DRG code	Unit cost/DRG tariff
████	████	████
████	████	████
████	████	████

## 11.6 Subsequent treatment costs

Not relevant.

## 11.7 Patient costs

This section includes the costs for:

- patient time transportation costs to GP
- transportation costs to the hospital
- patient time costs for hospital visits
- patient time costs for hospital visits

The unit cost of DKK 203/hour (18) is used, while the time use per visit or transport is assumed. See the Technical Report, section 4.7.7 for all details of distances and costs.

**Table 27 Patient costs used in the model**

Activity	Time spent [hours]
<b>Hospitalizations</b>	
Time for transportation each direction (x2)	████
Time for per outpatient visit	████
Patients time per day for inpatient visits	████



Activity	Time spent [hours]
Visit in primary care	
Time for transportation each direction (x2)	████████
Time for visits	████████

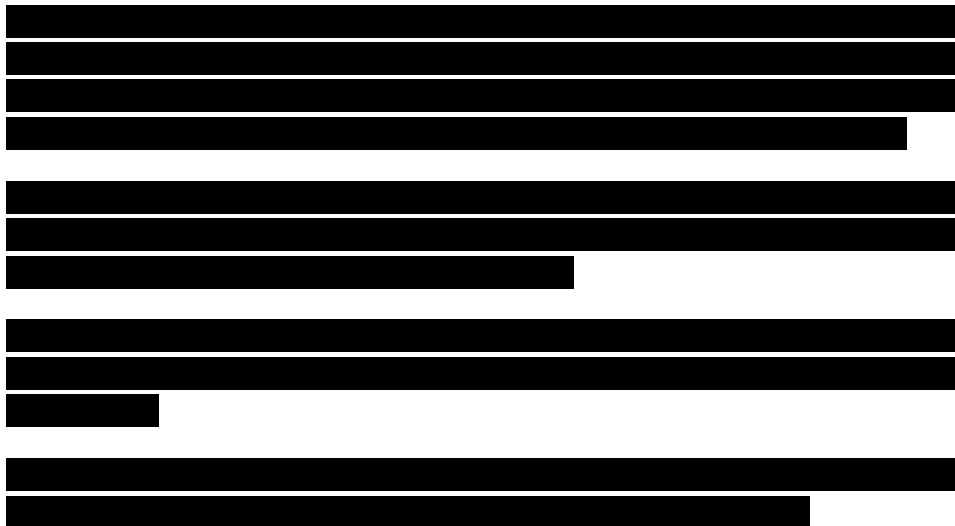
Source: Assumptions

## 11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

This is unchanged from the original model:

Patients who transition to the death health state incur a one-time cost for end of life, taking into consideration the costs for palliative care in the last month of life. The cost is set to the DRG rate for 30 days of palliative care (DRG tariff 2023 code: 05MA04 - Cost of 30 days palliative care for an HF patient) which equals DKK 66,885.

# 12. Results



## 12.1 Base case overview

Table 28 Base case overview

Feature	Description
Comparator	Placebo



Feature	Description
Type of model	Cost-utility analysis. Multi-state, cohort Markov model
Time horizon	30 years (expected remaining lifetime)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	HRQoL was measured with EQ-5D-3L in the pivotal phase 3 trial but converted to EQ-5D-5L data using validated methods from van Hout et al (16) and then converted to Danish utility values using weights from Jensen et al (17).
Costs included	Drug costs Hospitalization costs Costs of adverse events Background management costs Patient costs Transportation costs End of life costs
Dosage of medicine	Tafamidis: 61 mg orally once daily.
Average time on treatment	Tafamidis: ██████████ Placebo: █
Parametric function for PFS	Not relevant
Parametric function for OS	Tafamidis: Gamma Placebo: Gompertz
Inclusion of waste	Not included
Average time in model health state:	████████████████████
NYHA I	████████████████████
NYHA II	████████████████████
NYHA III	████████████████████
NYHA IV	████████████████████
Death	████████████████████



### 12.1.1 Base case results

**Table 29** Base case results, discounted estimates

	Tafamidis	Placebo	Difference
Medicine costs	████	████	████
Medicine costs – co-administration	████	████	████
Administration	████	████	████
Hospitalization costs	████	████	████
Background management costs	████	████	████
Costs associated with management of adverse events	████	████	████
Subsequent treatment costs	████	████	████
Patient costs	████	████	████
Transportation costs	████	████	████
End of life costs	████	████	████
<b>Total costs</b>	████	████	████
Life years gained NYHA I	████	████	████
Life years gained NYHA II	████	████	████
Life years gained NYHA III	████	████	████
Life years gained NYHA IV	████	████	████
<b>Total life years</b>	████	████	████
QALYs gained NYHA I	████	████	████
QALYs gained NYHA II	████	████	████
QALYs gained NYHA III	████	████	████
QALYs gained NYHA IV	████	████	████
QALYs (adverse reactions)	████	████	████
<b>Total QALYs</b>	████	████	████



	Tafamidis	Placebo	Difference
Incremental costs per life year gained			██████████
Incremental cost per QALY gained (ICER)			██████████

## 12.2 Sensitivity analyses



### 12.2.1 Deterministic sensitivity analyses

Figure 10 ██████████





**Table 30 One-way sensitivity analyses results**

	Change	Reason	Incremental cost (DKK)		Incremental benefit (QALYs)		ICER (DKK/QALY)	
			Low	High	Low	High	Low	High
ATTRwt base case	-	-	■		2.80		■	
Cost of AE, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Cost of AE, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-I, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-I, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-II, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-II, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-III, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-III, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-IV, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Background cost NYHA-IV, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■



	Change	Reason	Incremental cost (DKK)		Incremental benefit (QALYs)		ICER (DKK/QALY)	
			Low	High	Low	High	Low	High
Episode cost of CV-related hospitalization in NYHA I - placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-II, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-III, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-IV, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-I, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-II, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-III, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Episode cost of CV-related hospitalization in NYHA-IV, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
End of life cost	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■





	Change	Reason	Incremental cost (DKK)		Incremental benefit (QALYs)		ICER (DKK/QALY)	
			Low	High	Low	High	Low	High
CV-related hospitalization rate in NYHA-I, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-II, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-III, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-IV, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-I, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-II, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-III, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
CV-related hospitalization rate in NYHA-IV, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Cost discount rate	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
Health effects discount rate	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-I utility, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-II utility, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■



	Change	Reason	Incremental cost (DKK)		Incremental benefit (QALYs)		ICER (DKK/QALY)	
			Low	High	Low	High	Low	High
NYHA-III utility, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-IV utility, placebo	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-I utility, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-II utility, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-III utility, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
NYHA-IV utility, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■
PPP, tafamidis	-/+ 20%	See table note <sup>1</sup>	■	■	■	■	■	■

<sup>1</sup>To assess the impact of reducing/increasing the value of this parameter.



### 12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. Several parameters in the model are not necessarily fixed values but possess a certain variability. This variability was approximated through the PSA. The PSA evaluated the economic results when several parameters of the model were varied simultaneously. The specific parameters included in the PSA can be found in the Excel model on the sheet “PSA Inputs”. An overview of the PSA data is provided in Appendix G.

■ presents the cost-effectiveness plane, and Figure 12 illustrates the cost-effectiveness probability at different willingness-to-pay (WTP) thresholds. The mean ICER in the PSA analysis was ■.

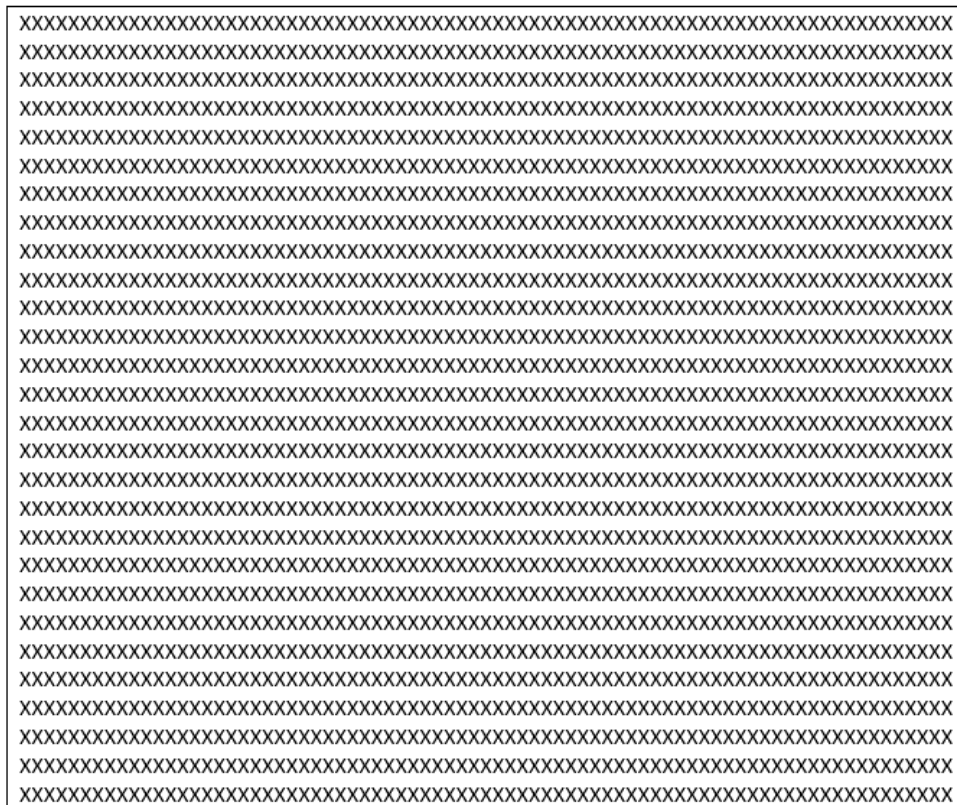


Figure 11 ■

■



Figure 12 [Redacted]

## 13. Budget impact analysis

Please see the Technical Report, section 7, for details on assumptions and inputs.



### Number of patients (including assumptions of market share)

Table 31 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Tafamidis	■	■	■	■	■
Placebo	■	■	■	■	■



	Year 1	Year 2	Year 3	Year 4	Year 5
Non-recommendation					
Tafamidis	■	■	■	■	■
Placebo	■	■	■	■	■

### Budget impact

Table 32 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	■	■	■	■	■
The medicine under consideration is NOT recommended	■	■	■	■	■
Budget impact of the recommendation	■	■	■	■	■

## 14. List of experts

Professor Steen Hvitfeldt Poulsen (SHP) from Aarhus University Hospital and Professor Finn Gustafsson (FG) from Rigshospitalet, have been consulted in connection with this application for reassessment to reaffirm the patient population size.

For any previous input from clinical experts, please see the original reimbursement application and the Technical Report.



## 15. References

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17. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy.* 2021;19(4):579-91.
18. Medicinrådet. Værdisætning af enhedsomkostninger, version 1.6. 2022.
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# Appendix A. Main characteristics of studies included

**Table 33 Main characteristic of studies included**

Trial name: Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)		NCT number: NCT01994889
<b>Objective</b>	Please see table 18 in the original application.	
<b>Publications – title, author, journal, year</b>	Since the original application (submitted May 2020), the following publications have been published: <ul style="list-style-type: none"><li>• Extrapolation of survival benefits in patients with transthyretin amyloid cardiomyopathy receiving tafamidis: analysis of the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. Li B, Alvir J, Stewart M. <i>Cardiol Ther.</i> 9:535-540. 2020.</li><li>• Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R <i>Eur J Heart Fail.</i> 23(2):277-285. 2021.</li><li>• Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS. <i>Am J Cardiol.</i> 141:98-105. 2021.</li><li>• Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, Boman K, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS. <i>JACC Heart Fail.</i> 9(2):115-123. 2021.</li><li>• Causes of cardiovascular hospitalization and death in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial [ATTR-ACT]). Miller AB, Januzzi JL, O’Neill BJ, Gundapaneni B, Patterson TA, Sultan MB, Lopez-Sendon J. <i>Am J Cardiol.</i> 148:146-150. 2021.</li><li>• Modeling of Survival and Frequency of Cardiovascular-Related Hospitalization in Patients with Transthyretin Amyloid Cardiomyopathy Treated with Tafamidis. Vong, C., Boucher, M., Riley, S., Harnisch LO. <i>Am J Cardiovasc Drugs.</i> 21:535–543. 2021</li><li>• Health impact of tafamidis in transthyretin amyloid cardiomyopathy patients: an analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the open-label long-term extension studies. Rozenbaum MH, Garcia A, Grima D, Tran D, Bhambri R, Stewart M, Li B, Heeg B, Postma M, Masri A. <i>Eur Heart J Qual Care Clin Outcomes.</i> 8:529-538. 2021.</li></ul>	





**Trial name: Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)**

**NCT number:  
NCT01994889**

- Natural history and progression of transthyretin amyloid cardiomyopathy: insights from (ATTR-ACT). Nativi-Nicolau J, Judge DP, Hoffman JE, Gundapaneni B, Keohane D, Sultan MB, Grogan M. *ESC Heart Failure*. 8:3875-3884. 2021.
- Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). Rozenbaum MH, Large S, Bhambri R, Stewart M, Young R, van Doornewaard A, Dasgupta N, Masri A, Nativi-Nicolau J. *J Compar Effect Res*. 10(11):927-938. 2021.
- Estimating the Effect of Tafamidis on Cardiovascular-Related Hospitalization in NYHA Class III Patients with Transthyretin Amyloid Cardiomyopathy in the Presence of Death. Li H, Rozenbaum M, Casey M, Sultan MB. *Cardiology*. 147(4):398-405. 2022.
- Relationship of binding-site occupancy, transthyretin stabilisation and disease modification in patients with tafamidis-treated transthyretin amyloid cardiomyopathy. Tess DA, Maurer TS, Li Z, Bulawa C, Fleming J, Moody AT. *Amyloid*.30(2):208-219. 2023.
- Improvements in efficacy measures with tafamidis in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). Hanna M, Fine N, Gundapaneni B, Sultan M. Witteles R. *JACC: Advances*. 1(5):1-8. 2022.
- Annual cardiovascular-related hospitalization days avoided with tafamidis in patients with transthyretin amyloid cardiomyopathy. Rozenbaum M, Tran D, Bhambri R, Nativi-Nicolau J. *Am J Cardiovasc Drugs*. 22(4):445-450. 2022.
- Association of Tafamidis With Health Status in Patients With ATTR Cardiac Amyloidosis: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. Sperry BW, Hanna M, Maurer MS, Nativi-Nicolau J, Floden L, Stewart M, Wyrwich KW, Barsdorf AI, Kapadia H, Spertus JA. *JAMA Cardiol*. 8(3):275-280. 2023.
- Tafamidis and quality of life in people with transthyretin amyloid cardiomyopathy in the study ATTR-ACT: A plain language summary. Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Sultan MB, Maurer MS. *Future Cardiol*. 18(3):165-172. 2022.
- Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study. Garcia-Pavia P, Sultan MB, Gundapaneni B, Sekijima Y, Perfetto F, Hanna M, Witteles R. *JACC: Heart Failure*. 12(1):150-160. 2023.
- Effect of Tafamidis on Cardiac Function in Patients With Transthyretin Amyloid Cardiomyopathy: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. Shah S, Fine N, Garcia-Pavia P, Klein A, Fernandes F, Weissman N, Maurer M, Boman K, Gundapaneni B, Sultan MB, Elliott P. *JAMA Cardiol*. 9(1):25-34. 2023.



<b>Trial name: Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)</b>		<b>NCT number: NCT01994889</b>
<b>Study type and design</b>	Please see the original application.	
<b>Sample size (n)</b>	441 patients (tafamidis n = 264, placebo n = 177)	
<b>Main inclusion criteria</b>	Please see the original application.	
<b>Main exclusion criteria</b>	Please see the original application.	
<b>Intervention</b>	Please see the original application.	
<b>Comparator(s)</b>	Please see the original application.	
<b>Follow-up time</b>	Please see the original application.	
<b>Is the study used in the health economic model?</b>	Yes.	
<b>Primary, secondary, and exploratory endpoints</b>	<p>Please see the original application for a description of primary and secondary endpoints.</p> <p><b>Endpoints included in this application:</b></p> <p>HRQoL, assessed as the change from baseline at each time point in EQ-5D-3L Index Score and EQ-VAS scores, was included as one of the exploratory end points in the ATTR-ACT study.</p>	
<b>Method of analysis</b>	<p>The analyses were carried out on the intent-to-treat (ITT) population, which included all patients who were enrolled, received at least 1 dose of tafamidis or placebo, and had at least 1 after-baseline efficacy evaluation.</p> <p>Changes in EQ-5D-3L Index Score and EQ-VAS at each time point were prespecified exploratory end points. Continuous variables were analyzed using a mixed model, repeated measures analysis of covariance with an unstructured covariance matrix; center and patient within center as random effects; treatment, visit, <i>TTR</i> genotype (ATTRm and ATTRwt), and visit by treatment interaction as fixed effects; and baseline score as covariate (20). There was no imputation of missing values.</p> <p>Please see the original application for the methods applied regarding other end points.</p>	
<b>Subgroup analyses</b>	None	
<b>Other relevant information</b>	None	



**Trial name: Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy**

**NCT number:  
NCT02791230**

**Objective** To evaluate the safety of daily oral dosing of tafamidis meglumine 20 mg or 80 mg (or tafamidis free acid 61 mg) in subjects diagnosed with transthyretin cardiomyopathy.

**Publications – title, author, journal, year**

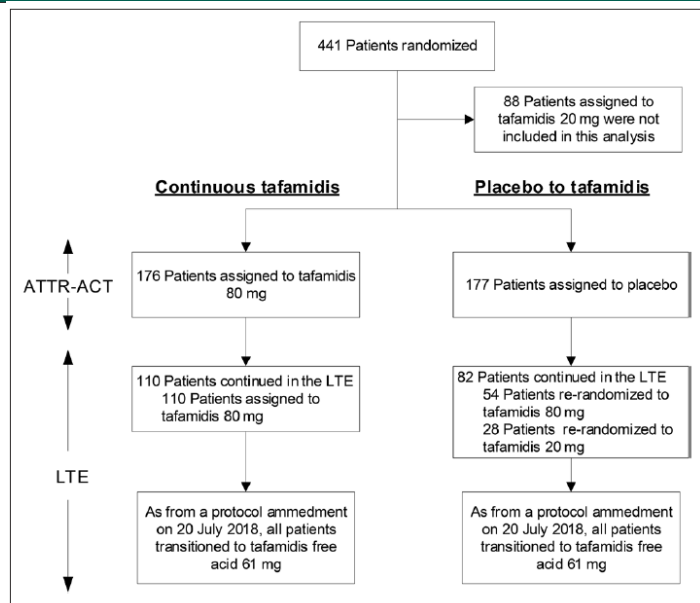
- Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R. *Eur J Heart Fail.* 23(2):277-285. 2021.
- Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). Rozenbaum MH, Large S, Bhambri R, Stewart M, Young R, van Doornewaard A, Dasgupta N, Masri A, Nativi-Nicolau J. *J Compar Effect Res.* 10(11):927-938. 2021.
- Reply to: Letter regarding the article 'Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study'. Damy T, Sultan MB, Witteles R. *Eur J Heart Fail.* 23(6):1057-1058. 2021.
- Health impact of tafamidis in transthyretin amyloid cardiomyopathy patients: an analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the open-label long-term extension studies. Rozenbaum MH, Garcia A, Grima D, Tran D, Bhambri R, Stewart M, Li B, Heeg B, Postma M, Masri A. *Eur Heart J Qual Care Clin Outcomes.* 8(5):529-538. 2022.
- Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB, Shah SJ. *Circ Heart Fail.* 15(1):4-11. 2022.
- Response by Elliott et al to Letter Regarding Article "Long-Term Survival with Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy". Elliott P, Gundapaneni B, Sultan MB. *Circulation Heart Failure.* 15(7):740-741. 2022.
- Long-term survival in people with transthyretin amyloid cardiomyopathy who took tafamidis: A Plain Language Summary. Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB, Shah SJ. *Future Cardiol.* 19(1):7-17. 2023.
- Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. *Eur J Heart Fail.* 25(11):2060-2064. 2023.
- Response by Elliott et al to Letter Regarding Article: Effects of Tafamidis on Heart Failure Hospitalization: The Tale of The Dog That



<b>Trial name: Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy</b>	<b>NCT number: NCT02791230</b>
	<p>Did Not Bark. Elliott P, Gundapaneni B, Garcia-Pavia P. Eur J Heart Fail. 2023.</p> <ul style="list-style-type: none"><li>• Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study. Garcia-Pavia P, Sultan MB, Gundapaneni B, Sekijima Y, Peretto F, Hanna M, Witteles R. JACC Heart Fail. 12(1):150-160. 2023.</li></ul>
<b>Study type and design</b>	<p>Global Phase 3, open label long-term extension safety study.</p> <p>Patients who completed 30 months' treatment in the ATTR-ACT study could enroll in the ongoing ATTR-ACT LTE study (NCT02791230) for up to 60 months.</p> <p>Patients receiving tafamidis (80 or 20 mg meglumine) in the ATTR-ACT study initially continued this dose in the ATTR-ACT LTE study. Patients receiving placebo in the ATTR-ACT study were randomized 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype (ATTRwt or ATTRm).</p> <p>A dose reduction could be requested if patients experienced adverse events, and patients receiving 80 mg could have their dose reduced to 20 mg.</p> <p>As of July 20, 2018, the ATTR-ACT LTE protocol was amended to transition all patients to tafamidis free acid 61 mg (a new, single-capsule formulation bioequivalent to tafamidis meglumine 80 mg). The transition to tafamidis free acid 61 mg followed the protocol amendment date, not a specified duration of treatment, with patients treated with tafamidis 80 or 20 mg (in ATTR-ACT and the ATTR-ACT LTE study up to the protocol amendment) for a median of 39 months.</p> <p>The ATTR-ACT LTE study is ongoing.</p>
<b>Sample size (n)</b>	<p>In the ATTR-ACT study, 176 and 177 patients were assigned to tafamidis 80 mg and placebo, respectively. Of these, 110/176 patients treated with tafamidis 80 mg and 82/177 treated with placebo in the ATTR-ACT study subsequently enrolled and received tafamidis in the ATTR-ACT LTE study.</p> <p>An illustration of the flow of patients included in the analysis of clinical efficacy in the current application is provided below.</p>



**Trial name: Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy** **NCT number: NCT02791230**



<b>Main inclusion criteria</b>	<p>Cohort A: Completion of 30 months of study treatment on Pfizer Protocol B3461028 (ATTR-ACT). Data from this cohort forms the basis of the results published by Elliott et al. (1, 2) and the basis for the current application.</p> <p>Cohort B: Patients in specific countries (Australia, Argentina, Belgium, Canada, Czech Republic, France, Hong Kong, Japan, Netherlands, Spain, Sweden, Taiwan and United States) diagnosed with ATTR-CM who did not previously participate in Pfizer Study B3461028. The purpose of this cohort was to provide these patients early access to tafamidis, until local availability by prescription for the ATTR-CM indication.</p>
<b>Main exclusion criteria</b>	Liver and/or heart transplant, or implanted cardiac mechanical assist device
<b>Intervention</b>	<p>Tafamidis 80 mg or 20 mg once daily.</p> <p>Following a protocol amendment in July 2018, patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg.</p> <p>110 patients treated with tafamidis 80 mg and 82 treated with placebo in the ATTR-ACT study subsequently enrolled and received tafamidis in the ATTR-ACT LTE study.</p>
<b>Comparator(s)</b>	There was no comparator, as the ATTR-ACT LTE study was open-label.
<b>Follow-up time</b>	At the latest data cut-off (August 1, 2021), the median follow-up time from ATTR-ACT baseline to the LTE study interim analysis was 61 months for patients in the continuous tafamidis group and 59 months for those in the placebo to tafamidis group.



**Trial name: Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy** **NCT number: NCT02791230**

**Is the study used in the health economic model?** Yes.

**Primary, secondary and exploratory endpoints** The primary endpoints were all-cause mortality and incidence of treatment emergent adverse events.

Other pre-specified endpoints were:

- Cardiovascular-related mortality
- All-cause hospitalization
- Cardiovascular-related hospitalization
- Kansas City Cardiomyopathy Questionnaire
- New York Heart Association classification
- Body Mass Index/modified Body Mass Index
- Cardiac biomarkers (NT-proBNP and Troponin I)

Endpoints included in this application are all-cause mortality and safety.

**Method of analysis** The primary efficacy outcome in the ATTR-ACT LTE study was all-cause mortality, with heart transplant and implantation of a cardiac mechanical assist device treated as death.

Differential all-cause mortality in the 2 groups was assessed by Cox proportional hazards model with treatment, genotype (ATTRwt and ATTRm), and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in the model.

Mortality was also assessed by Cox proportional hazards model by genotype (ATTRm and ATTRwt) and by NYHA baseline classification (NYHA class I or II and NYHA class III).

The extrapolated placebo group was constructed from a gamma model based on patient-level data from placebo-treated patients in the ATTR-ACT study.

Other models that provided good statistical fit were evaluated to extrapolate survival beyond 30 months as described previously (10). Briefly, the analysis was conducted based on technical support guidelines from the National Institute for Health and Care Excellence, with multiple models applied to systematically fit different candidate curves to the patient-level data from the ATTR-ACT study. The candidate curves were evaluated following the model evaluation procedure recommended in the guideline (21) with the gamma distribution selected here (10).

**Subgroup analyses** Please see the initial application.

**Other relevant information** None.



## Appendix B. Efficacy results per study

### Results per study

Table 34 Results per study

Results of ATTR-ACT LTE (NCT02791230)*											
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Median OS (months)	Continuous tafamidis	176	67.0 (47.0–N/E)	31.2 <sup>†</sup>	-	-	-	-	-	The median survival is based on the Kaplan-Meier estimator.	(1)
All patients (ATTRwt and ATTRm)	Placebo to tafamidis	177	35.8 (29.7–41.1)								
All-cause mortality, (%)	Continuous tafamidis	176	44.9	-17.8 <sup>†</sup>	-	-	HR: 0.59	0.44–0.79	<0.001	The primary efficacy outcome in the ATTR-ACT LTE study was all-cause mortality, with heart transplant and implantation of a cardiac mechanical assist device treated as death. Differential all-cause mortality in the 2 groups was assessed by Cox proportional hazards model with treatment, genotype (ATTRwt and ATTRm), and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in the model. Mortality was also assessed by Cox proportional hazards model by	(1)
All patients (ATTRwt and ATTRm)	Placebo to tafamidis	177	62.7								



Results of ATTR-ACT LTE (NCT02791230)\*

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
genotype (ATTRm and ATTRwt) and by NYHA baseline classification (NYHA class I or II and NYHA class III).											
Kaplan–Meier preliminary estimates of 5-year survival, %  All patients (ATTRwt and ATTRm)	Continuous tafamidis 80/61 mg	176	53.2	20.8 <sup>st</sup>	-	-	-	-	-	Preliminary 5-year survival rate was based on the longest available data from the data-cut. As the LTE study is ongoing, no details on the calculation are available at this time.	(1)
	Placebo to tafamidis 80/61 mg	177	32.4								
Median OS, months  Patients with ATTRwt	Continuous tafamidis 80/61 mg	134	67.0 (54.4–N/E)	28.4 <sup>st</sup>	-	-	-	-	-	The median survival is based on the Kaplan-Meier estimator.	(1)
	Placebo to tafamidis 80/61 mg	134	38.6 (34.1–47.1)								
All-cause mortality, %	Continuous tafamidis 80/61 mg	134	40.3	-19.4 <sup>st</sup>	-	-	HR: 0.61	0.43–0.87	0.006	The primary efficacy outcome in the LTE study was all-cause mortality, with heart transplant and implantation of a cardiac mechanical assist device	(1)





Results of ATTR-ACT LTE (NCT02791230)\*

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Patients with ATTRwt	Placebo to tafamidis 80/61 mg	134	59.7							treated as death. Differential all-cause mortality in the 2 groups was assessed by Cox proportional hazards model with treatment, genotype (ATTRwt and ATTRm), and NYHA baseline classification (NYHA classes I and II combined and NYHA class III) in the model. Mortality was also assessed by Cox proportional hazards model by genotype (ATTRm and ATTRwt) and by NYHA baseline classification (NYHA class I or II and NYHA class III).	
Kaplan–Meier preliminary estimates of 5-year survival, %	Continuous tafamidis 80/61 mg	134	57.8	21.5 <sup>†</sup>	-	-	-	-	-	Preliminary survival rate was based on the longest available data from the data-cut. As the LTE study is ongoing, no details on the calculation are available at this time.	(1)
	Placebo to tafamidis 80/61 mg	134	36.3								
All-cause mortality, %	Continuous tafamidis 80/61 mg	121	40.5	-20.9 <sup>†</sup>	-	-	HR: 0.50	0.35–0.73	0.0003	All-cause mortality was assessed for each NYHA group (I/II or III) using a Cox proportional hazards model with treatment and genotype included in the	(2)



Results of ATTR-ACT LTE (NCT02791230)*											
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Patients in NYHA class I/II	Placebo to tafamidis 80/61 mg	114	61.4							model. Heart transplantation or implantation of a mechanical ventricular assist device were considered equivalent to death.	
All-cause mortality, %	Continuous tafamidis 80/61 mg	55	63.6	-16.4 <sup>a</sup>	-	-	HR: 0.64	0.41–0.99	0.0460		
Patients in NYHA class III	Placebo to tafamidis 80/61 mg	63	81.0								

\* As the ATTR-ACT LTE study is ongoing, not all results are currently available. <sup>a</sup>Values have not been published and have been calculated by us for the current application. N/E, nonestimable

## Appendix C. Comparative analysis of efficacy

Not applicable, as analysis of efficacy is based on a single head-to-head study.



# Appendix D. Extrapolation

## D.1 Extrapolation of all-cause OS

### D.1.1 Data input

The proportion of patients who dies in each cycle is informed by the mortality data from the KM curve from the ATTR-ACT study, and the model will correct study OS for background general population mortality. Please see Technical Report, section 4.6.1, for the full explanation.

The model determines OS for the full subpopulation chosen (i.e., ATTRwt) pooled across all NYHA classes. Data up to 30 months of follow-up were available from the ATTR-ACT study for placebo and tafamidis (11). From the ATTR-ACT LTE study, additional data up to [REDACTED] months of follow-up [REDACTED] were available for tafamidis (4). Only data up to 30 months from the ITT analysis of ATTR-ACT were used for placebo. Since the treatment-specific OS curves were already diverging at 18 months from first dose (11), there was no concern with using more follow-up time for tafamidis than for placebo.

### D.1.2 Model

Briefly, to extrapolate the KM survival curves to a lifetime horizon for the model, seven standard parametric survival models were curve fit to the individual patient data from the ATTR-ACT study in accordance with the best practices from NICE Technical Support Document 14 for survival analysis alongside clinical trials (21). Parameters and model fit statistics were calculated for each curve type. For the full explanation, please see the Technical Report, section 4.6.1.

If by visual inspection all the extrapolations appeared to generally fit the KM data well, the most appropriate curve for data extrapolation was selected based on the following:

- Clinical validity:
  - By comparing the extrapolated outcomes to published data, general population life expectancy, and validation with a clinical expert.
  - The extrapolated curve must be clinically meaningful.
- The goodness of fit for each parametric survival function based on statistical analyses of AIC and BIC and the log cumulative hazard plots.

According to the NICE extrapolation guidelines, fitting separate parametric models to each treatment arm involves fewer assumptions and is a justified approach when the extrapolation uses patient-level data (21).

### D.1.3 Proportional hazards

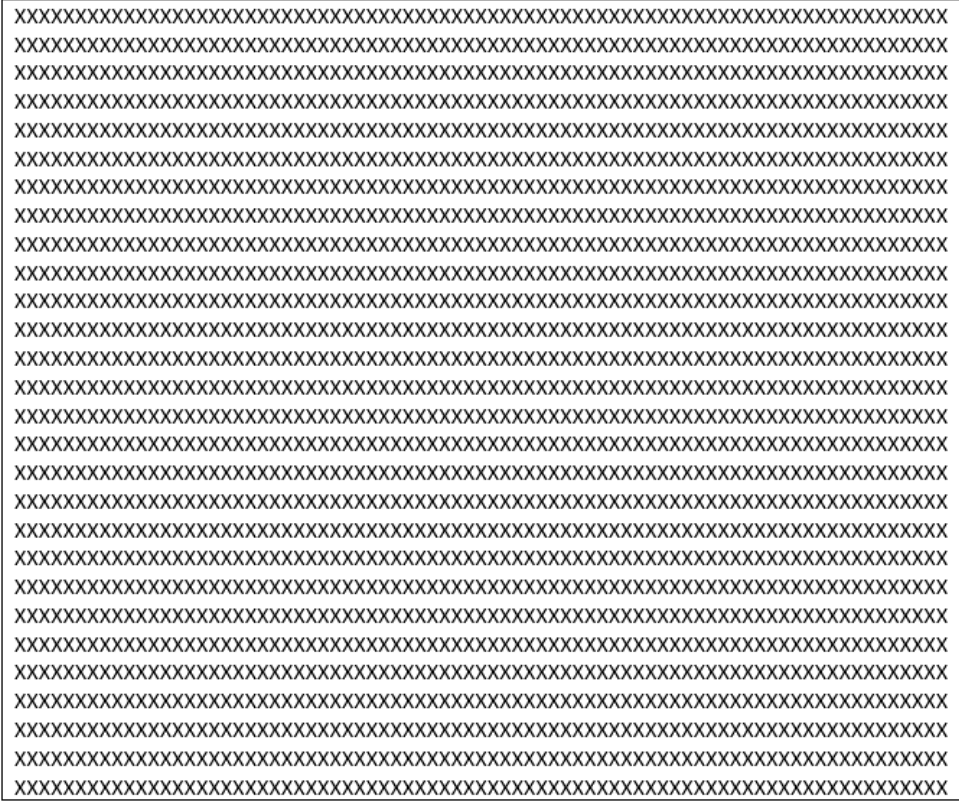


Figure 13 

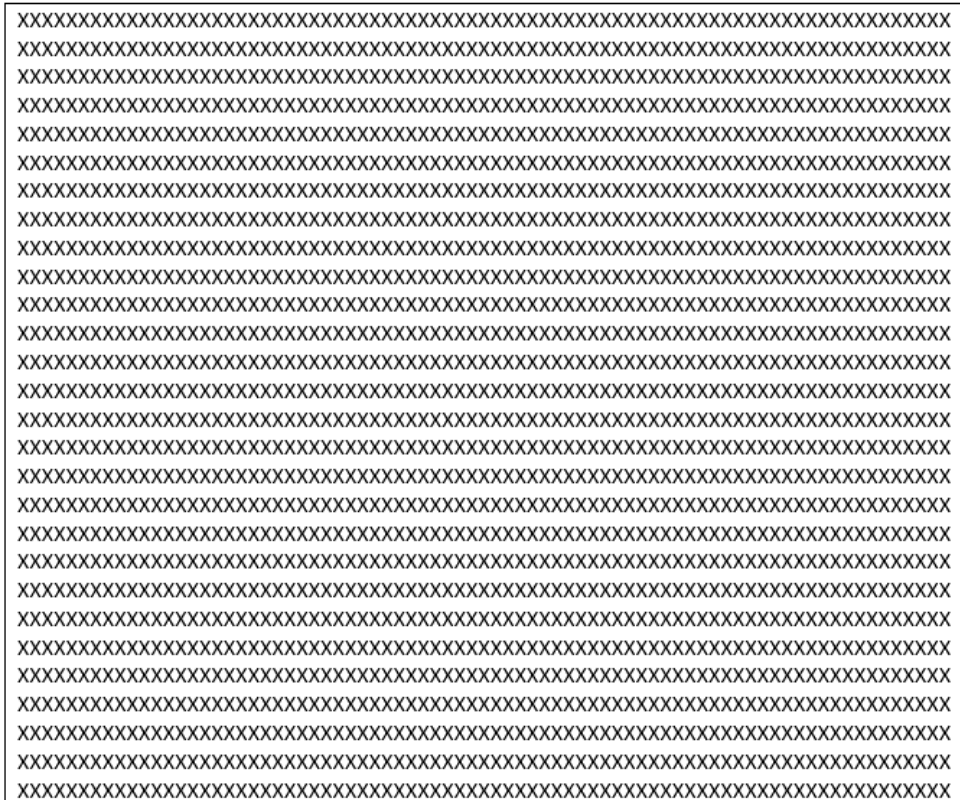


Figure 14 [REDACTED]



Figure 15 [REDACTED]

#### D.1.4 Evaluation of statistical fit

Table 35 [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



#### D.1.5 Evaluation of visual fit

For evaluation of visual fit, please see Technical Report, section 4.6.1 for each extrapolation.

#### D.1.6 Evaluation of hazard functions

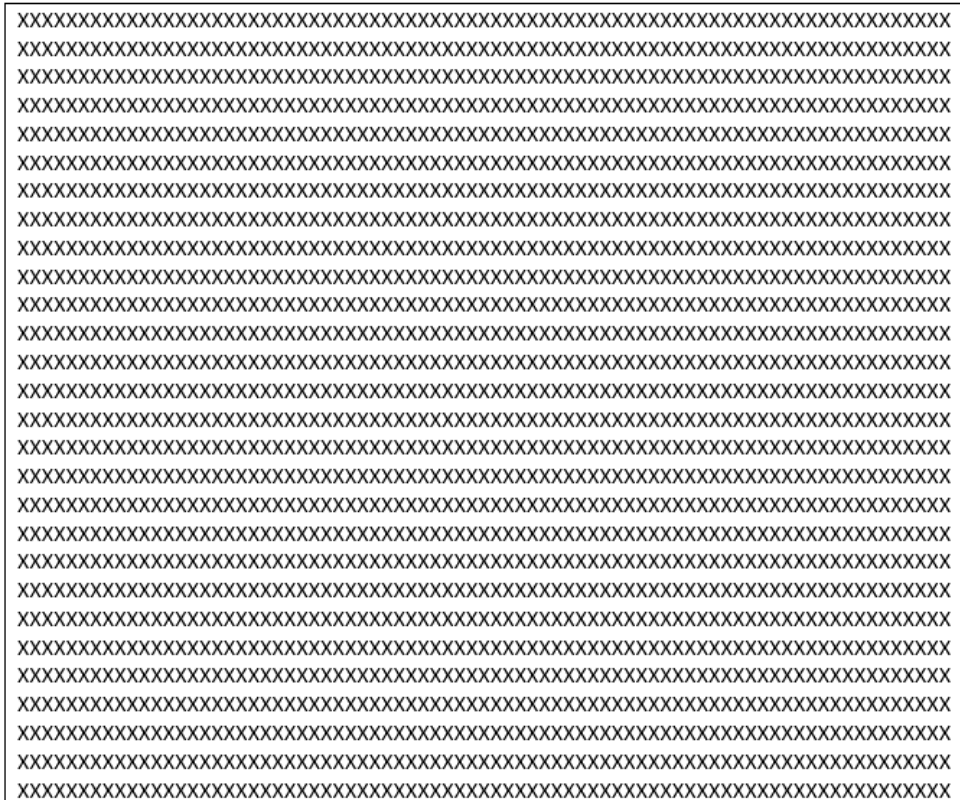


Figure 16 [REDACTED]



**Figure 17** [REDACTED]

For discussion of the functions and for other extrapolations, please see the Technical Report, section 4.6.1.

#### **D.1.7 Validation and discussion of extrapolated curves**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### **D.1.8 Adjustment of background mortality**





Figure 18 [Redacted]

[Redacted]



**Figure 19** [Redacted]

**D.1.9 Adjustment for treatment switching/cross-over**

Not applicable.

**D.1.10 Waning effect**

Not applicable.

**D.1.11 Cure-point**

Not applicable.

**D.2 Extrapolation of [effect measure 2]**

Not applicable.



## Appendix E. Serious adverse events

Please see the original application for a list of serious adverse events.

## Appendix F. Health-related quality of life

Not applicable, as no domain specific data is relevant for this application.



# Appendix G. Probabilistic sensitivity analyses

Table 36 presents an overview of all the parameters included in the PSA. All parameters relevant for the present analysis were included in the PSA. The assumptions and data for the PSA can be found in the model on the 'PSA inputs' sheet.

**Table 36. Overview of parameters in the PSA**

Input parameter	Point estimate	SE	Probability distribution
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■



Input parameter	Point estimate	SE	Probability distribution
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
██████████	■	■	■
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██████████	■	■	■
██████████	■	■	■
██████████	■	■	■



Input parameter	Point estimate	SE	Probability distribution
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



Input parameter	Point estimate	SE	Probability distribution
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■
[REDACTED]	■	■	■

## Appendix H. Literature searches for the clinical assessment

Not applicable, as the included clinical data is based on the ATTR-ACT study which is a head-to-head study comparing tafamidis with placebo.

### H.1.1 Unpublished data

The input into the health economic model is derived from the ATTR-ACT study and its long-term extension, whose results are published. However, unpublished data, i.e., data on file, is used in the health economic application when the published data is not in the form needed to populate the model. For example, when data is only published for ATTR-CM, not ATTRwt specifically.





## Appendix I. Literature searches for health-related quality of life

Not applicable, as the included clinical data is based on the ATTR-ACT study which is a head-to-head study comparing tafamidis with placebo.

### I.1.1 Unpublished data

[Redacted]

[Redacted]

## Appendix J. Literature searches for input to the health economic model

### J.1 External literature for input to the health economic model

This section is not relevant, since no new literature was added to the health economic application since the previous application.



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