IQWiG Reports – Commission No. A20-102

Tafamidis (transthyretin amyloid cardiomyopathy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tafamidis (Transthyretin-Amyloidose mit Kardiomyopathie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
AE	adverse event
ACT	appropriate comparator therapy
ATTR-CM	transthyretin amyloid cardiomyopathy
BSC	best supportive care
CI	confidence interval
EAC	Endpoint Adjudication Committee
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
InGef	Institut für angewandte Gesundheitsforschung Berlin (Institute for applied healthcare research Berlin)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OSS	overall summary score
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
TTR	transthyretin
VAS	visual analogue scale
6 MWT	6-minute walking test

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tafamidis. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 November 2020.

Research question

The aim of the present report is the assessment of the added benefit of tafamidis in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of tafamidis

Research question	Therapeutic indication	ACT[a]
1	Wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients	Best supportive care[b, c, d]

a. Presentation of the ACT specified by the G-BA.
b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hATTR amyloidosis, and is documented as concomitant treatment.
d. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloid cardiomyopathy; G-BA: Federal Joint Committee; hATTR: hereditary transthyretin amyloidosis

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum study duration of 24 weeks were used for the derivation of the added benefit.

Study pool and study characteristics

The study pool for the benefit assessment of tafamidis in comparison with the ACT consists of the RCT ATTR-ACT.

The ATTR-ACT study is a multicentre, double-blind, 3-arm RCT comparing 2 different dosages of tafamidis, each + BSC, with placebo + BSC. Tafamidis was available in the study as tafamidis meglumine in a dosage of either 80 mg or 20 mg. The arm with the dosage of

80 mg tafamidis meglumine is used for the present dossier assessment. The arm with a dosage of 20 mg tafamidis meglumine is not considered below, as this dosage is only approved for the treatment of patients with transthyretin amyloid polyneuropathy.

The study included adult patients with wild type or hereditary ATTR-CM. Patients had to have cardiac failure requiring treatment with a diuretic. The cardiac failure had to be classified as New York Heart Association (NYHA) class I to III. Presence of amyloid had to be confirmed by biopsy.

After screening, patients were randomly assigned to the study arms, stratified by transthyretin (TTR) genotype and NYHA classification (intervention arm: 176 patients; comparator arm: 177 patients).

Treatment with tafamidis or placebo was carried out in each case in addition to concomitant symptomatic treatment, which included, for example, the treatment of cardiac failure with concomitant drug therapies. Heart and/or liver transplantation as well as implantation of a cardiac mechanical assist device was possible, but led to treatment discontinuation, and only vital status and transplantation status were documented until month 30.

The planned treatment duration was 30 months. Subsequently, the patients could participate in a 60-month extension study, in which all patients of the study received tafamidis meglumine (20 mg or 80 mg) or, depending on availability, tafamidis free acid (61 mg). Patients from the original placebo arm were randomly assigned to the 2 tafamidis arms.

The primary outcome of the study was a composite outcome of all-cause mortality and cardiovascular-related hospitalization. Patient-relevant secondary outcomes were all-cause mortality, cardiovascular hospitalization, endurance, health status, health-related quality of life, and adverse events (AEs).

Implementation of the appropriate comparator therapy

Patients in the ATTR-ACT study were allowed to continue taking the drugs they had been taking at a stable dose for 4 weeks before the start of the study. Diuretics could still be adjusted during the first 4 weeks of the study. It was possible for patients to start a new therapy after study start.

Overall, the present benefit assessment considers the concomitant therapy used in the ATTR-ACT study to be an adequate implementation of the ACT BSC.

Risk of bias

The risk of bias across outcomes was rated as low for the ATTR-ACT study.

The risk of bias was rated as low for the results of the following outcomes: all-cause mortality, health status, health-related quality of life, serious adverse events (SAEs), discontinuation due

to AEs, and dyspnoea. The results of the outcome "endurance" and the outcome "cardiovascular hospitalization" have a high risk of bias.

Results

Mortality

All-cause mortality

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "all-cause mortality". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

Morbidity

Cardiovascular hospitalization

For the outcome "cardiovascular hospitalization", there was a statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC for the total population based on the rate, but not based on patients with (at least one) event. However, there was an effect modification by the characteristic "NYHA classification" for both operationalizations. For patients with NYHA class I + II cardiac failure, this resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for the outcome "cardiovascular hospitalization". For patients with NYHA class III cardiac failure, in contrast, there was a hint of lesser benefit of tafamidis + BSC in comparison with BSC for this outcome.

Endurance (recorded with the 6-minute walking test [6 MWT])

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "endurance". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

Health status (recorded with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "health status". The standardized mean difference (SMD) in the form of Hedges' g was considered to assess the relevance of the result. The 95% confidence interval (CI) of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was an effect modification by the characteristic "TTR genotype". However, the results in the 2 subgroups did not differ in the direction of effect and in the extent from the result of the total study population, so that the characteristic was not considered further for the outcome "health status". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

Health-related quality of life

Health-related quality of life (recorded with the Kansas City Cardiomyopathy Questionnaire [KCCQ] overall summary score [OSS])

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "health-related quality of life". The SMD in the form of Hedges' g was considered to assess the relevance of the result. The 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

Side effects

Overall rates of SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "SAEs" or for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from tafamidis + BSC in comparison with BSC for either of these outcomes; greater or lesser harm is therefore not proven.

Dyspnoea (Preferred Term [PT], AE)

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "dyspnoea". However, there was an effect modification by the characteristic "NYHA classification". For patients with NYHA class I + II cardiac failure, this resulted in a hint of lesser harm of tafamidis + BSC in comparison with BSC for the outcome "dyspnoea". For patients with NYHA class III cardiac failure, in contrast, there was no hint of greater or lesser harm of tafamidis + BSC in comparison with BSC for this outcome; greater or lesser harm for this patient group is therefore not proven.

It is questionable whether the effect for the outcome "dyspnoea" (PT, AE) actually is to be assigned to the outcome category "side effects" or whether it rather reflects the clinical picture of the underlying disease.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug tafamidis in comparison with the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The overall picture shows both positive and negative effects of tafamidis + BSC in comparison with BSC, which are partly dependent on the characteristic of NYHA classification. For this reason, the positive and negative effects are assessed below separately for patients with NYHA class I + II cardiac failure and for patients with NYHA class III cardiac failure.

Patients with NYHA class I + II cardiac failure at baseline

There were only positive effects for patients with NYHA class I + II cardiac failure at baseline. These include effects of considerable extent (outcomes "all-cause mortality", "cardiovascular hospitalization" and "dyspnoea") and effects on several outcomes of non-quantifiable extent each. For the outcome "dyspnoea", however, it is questionable whether the effect for this outcome can actually be assigned to the outcome category of side effects or whether it does not rather reflect the clinical picture of the underlying disease.

In summary, there is a hint of considerable added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class I + II cardiac failure at baseline.

Patients with NYHA class III cardiac failure at baseline

There were both positive and negative effects for patients with NYHA class III cardiac failure at baseline. There was an advantage of considerable extent in all-cause mortality. There were further positive effects, each with a non-quantifiable added benefit, in the outcomes "endurance", "health status", and "health-related quality of life". However, these were accompanied by lesser benefit of minor extent in the outcome "cardiovascular hospitalization".

For the 2 outcomes "all-cause mortality" and "health-related quality of life" in particular, no subgroup analyses were prepared by the company for the operationalizations used in the benefit assessment. Considering the negative effect for the outcome "cardiovascular hospitalization" and the fact that subgroup analyses for the characteristic of NYHA classification were not available for all outcomes, it cannot be assessed whether there is any advantage at all or even lesser benefit for these outcomes in patients with NYHA class III cardiac failure.

In summary, there is no hint of an added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class III cardiac failure at baseline.

Table 3 shows a summary of probability and extent of the added benefit of tafamidis.

Table 3: Tafamidis – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients	Best supportive care[b, c, d]	▪ Patients with NYHA class I + II cardiac failure: hint of considerable added benefit ▪ Patients with NYHA class III cardiac failure: added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hATTR amyloidosis, and is documented as concomitant treatment.
d. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloid cardiomyopathy; G-BA: Federal Joint Committee; hATTR: hereditary transthyretin amyloidosis; NYHA: New York Heart Association

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of tafamidis in comparison with BSC as ACT in adult patients with ATTR-CM.

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of tafamidis

Research question	Therapeutic indication	ACT[a]
1	Wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients	Best supportive care[b, c, d]

a. Presentation of the ACT specified by the G-BA.
b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hATTR amyloidosis, and is documented as concomitant treatment.
d. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloid cardiomyopathy; G-BA: Federal Joint Committee; hATTR: hereditary transthyretin amyloidosis

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tafamidis (status: 15 October 2020)
- bibliographical literature search on tafamidis (last search on 15 October 2020)
- search in trial registries/trial results databases for studies on tafamidis (last search on 15 October 2020)
- search on the G-BA website for tafamidis (last search on 15 October 2020)

To check the completeness of the study pool:

- bibliographical literature search on tafamidis (last search on 3 December 2020)

The check did not identify any additional relevant studies.

2.3.1 **Studies included**

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tafamidis vs. BSC

Study	**Study category**			**Available sources**		
	Study for the approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**	**CSR (yes/no [citation])**	**Registry entries[b] (yes/no [citation])**	**Publication and other sources[c] yes/no [citation])**
B3461028 (ATTR-ACT[d])	Yes	Yes	No	No[e]	Yes [3,4]	Yes [5-10]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

2.3.2 **Study characteristics**

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ATTR-ACT	RCT, double-blind, parallel	Adult patients (≥ 18 and ≤ 90) with wild type[b] or hereditary[c] transthyretin amyloid cardiomyopathy with ▪ history of cardiac failure[d] requiring treatment with a diuretic ▪ NT-proBNP concentration ≥ 600 pg/mL at screening ▪ > 100 m on the 6 MWT at screening ▪ NYHA class I-III cardiac failure	Tafamidis 20 mg (N = 88)[e] tafamidis 80 mg (N = 176) placebo (N = 177)	Screening: up to 35 days Treatment: 30 months[f] Follow-up observation: up to 28 days	48 study centres in: Belgium, Brazil, Canada, Czech Republic, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, United Kingdom, USA 12/2013–2/2018	Primary: composite outcome of all-cause mortality or cardiovascular-related hospitalizations Secondary: all-cause mortality, cardiovascular hospitalization, endurance, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Defined by all of the following criteria: absence of a variant TTR genotype; evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac; TTR precursor protein identification by IHC, scintigraphy or mass spectrometry.
c. Defined by any of the following criteria: presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype; evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac.
d. With at least one prior hospitalization for cardiac failure or clinical evidence of cardiac failure (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures.
e. The treatment arm is not relevant for the assessment because the 20 mg dosage is only approved for transthyretin amyloid polyneuropathy and is no longer shown in the next tables.
f. After completion of treatment, patients could participate in an extension study for up to 60 months.

AE: adverse event; BSC: best supportive care; IHC: immunohistochemistry; N: number of randomized patients; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus; 6 MWT: 6-minute walking test

Table 7: Characteristics of the intervention – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study	Intervention	Comparison
ATTR-ACT	Tafamidis meglumine 80 mg[a] (4 x 20 mg tafamidis soft capsules), oral[b]	Placebo (4 x 20 mg soft capsules), oral[b]
	Treatment adjustment: ▪ blinded dose reduction to 40 mg (2 x 20 mg soft capsules) in case of intolerance ▪ if poor tolerability continued, the study medication could be discontinued	
	Non-permitted pretreatment ▪ heart and/or liver transplantation ▪ implantation of a cardiac mechanical assist device ▪ tafamidis **Permitted concomitant treatment** ▪ NSAIDs: only acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, sulindac; other NSAIDs require agreement with the sponsor or medical monitoring ▪ drugs indicated as standard of care, with stable treatment for 4 weeks prior to baseline (diuretics could be adjusted within the first 4 weeks of the study) **Non-permitted concomitant treatment** ▪ diflunisal and any investigational products (discontinued 30 days prior to baseline) ▪ tauroursodeoxycholate and doxycycline ▪ digitalis and calcium channel blockers (e.g. verapamil, diltiazem)	

a. Different formulation than in the SPC [11]; according to the SPC, the recommended dosage is 61 mg tafamidis free acid.
b. The capsules were to be taken every day in the morning at a constant time with a glass of water without chewing.

BSC: best supportive care; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Description of the ATTR-ACT study

The ATTR-ACT study is a multicentre, double-blind, 3-arm RCT comparing 2 different dosages of tafamidis, each + BSC, with placebo + BSC. Tafamidis was available in the study as tafamidis meglumine in a dosage of either 80 mg or 20 mg. The arm with the dosage of 80 mg tafamidis meglumine is used for the present dossier assessment (see also below, Section *Note on the formulation of tafamidis*). The arm with a dosage of 20 mg tafamidis meglumine is not considered below, as this dosage is only approved for the treatment of patients with transthyretin amyloid polyneuropathy.

The study included adult patients with wild type or hereditary ATTR-CM. Patients had to have cardiac failure requiring treatment with a diuretic, and the N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentration had to be ≥ 600 pg/mL. Presence of amyloid had to be confirmed by biopsy. Patients had to be able to complete a distance of at least 100 m in the 6 MWT, and their cardiac failure was not allowed to be classified as NYHA IV.

After screening, patients were randomly assigned to the study arms, stratified by TTR genotype and NYHA classification. 176 patients were randomized to the intervention arm (80 mg tafamidis meglumine) and 177 patients to the comparator arm (placebo).

In principle, administration of the study medication was in compliance with the requirements of the Summary of Product Characteristics (SPC) of tafamidis [11]. However, the patients in the study received 80 mg of tafamidis meglumine, whereas, according to the SPC, tafamidis is approved in a dosage of 61 mg free acid in the present therapeutic indication (see Section *Note on the formulation of tafamidis* for more details).

Treatment with tafamidis or placebo was carried out in each case in addition to concomitant symptomatic treatment, which included, for example, the treatment of cardiac failure with concomitant drug therapies. Heart and/or liver transplantation as well as implantation of a cardiac mechanical assist device was possible, but led to treatment discontinuation, and only vital status and transplantation status were documented until month 30. However, this affected only few patients (6 [3.4%] organ transplants and 2 [1.1%] implanted cardiac mechanical assist devices in the tafamidis arm versus 5 [2.8%] organ transplants in the placebo arm). It is assumed that transplantation was not an option for the other patients at the time of therapy with tafamidis.

The planned treatment duration was 30 months. Following the study, the patients could participate in a 60-month extension study, in which all patients of the study received tafamidis meglumine (20 mg or 80 mg) or, depending on availability, tafamidis free acid (61 mg). Patients from the original placebo arm were randomly assigned to the tafamidis arms.

The primary outcome of the ATTR-ACT study was a composite outcome of all-cause mortality and cardiovascular-related hospitalization. Patient-relevant secondary outcomes were all-cause mortality, cardiovascular hospitalization, endurance, health status, health-related quality of life, and AEs.

Note on the formulation of tafamidis

The dosage of 80 mg tafamidis meglumine used in the ATTR-ACT study deviates from the specifications of the SPC, according to which tafamidis is approved for the present therapeutic indication as free acid at a dosage of 61 mg [11].

The company explained in Module 4 B that the approved 61 mg tafamidis free acid is a new formulation that is bioequivalent to 80 mg tafamidis meglumine in the opinion of the company. The company cited 2 bioequivalence studies [12,13], which, according to the company, tested the bioequivalence to the 80 mg (4 times 20 mg) tafamidis meglumine formulation. Data from these studies have neither been published nor prepared by the company for the dossier.

According to the information provided in the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA), bioequivalence between 61 mg tafamidis free acid and 80 mg tafamidis meglumine was proven at steady state, but not after single dose, which,

according to the EMA, is required for evaluation of bioequivalence [14]. Therefore, from the EMA's point of view, it cannot be considered that bioequivalence has strictly been proven. EMA expresses serious concern, since most efficacy data come from tafamidis meglumine treatments. Due to the results on mortality and morbidity and all available data, the EMA agrees to approval of 61 mg tafamidis free acid in this specific case despite the concerns.

The formulation used in the study (meglumine instead of free acid) did not lead to the exclusion of the study from the benefit assessment, but this was taken into account in the certainty of conclusions of the results (see Section 2.4.3).

Implementation of the appropriate comparator therapy

The data on concomitant therapies given in the course of the study in ≥ 15 % in one of the study arms are presented in Table 8.

Table 8: Concomitant therapies in the course of the study in ≥ 15 % of the patients in at least one study arm – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC (multipage table)

Study **Category of concomitant therapy** **Concomitant therapy[a]** **Drugs[a]**	**Tafamidis + BSC** **N[b] = 176**	**Placebo + BSC** **N[b] = 177**
Study ATTR-ACT		
Non-drug interventions according to MedDRA, n (%)	157 (89.2)	145 (81.9)
Cardiac pacemaker insertion	28 (15.9)	25 (14.1)
Cardioversion	22 (12.5)	30 (16.9)
Implantable defibrillator insertion	18 (10.2)	26 (14.7)
Concomitant drug therapies according to WHO-DD[c], n (%)	176 (100)	176 (100)
Analgesics		
Acetylsalicylic acid	64 (36.4)	73 (41.2)
Paracetamol	71 (40.3)	71 (40.1)
Anaesthetics		
Lidocaine	32 (18.2)	28 (15.8)
Antibacterial agents for systemic application		
Ceftriaxone	14 (8.0)	27 (15.3)
Gout preparations		
Allopurinol	57 (32.4)	56 (31.6)
Antithrombotic agents		
Acetylsalicylic acid	64 (36.4)	73 (41.2)
Apixaban	35 (19.9)	37 (20.9)
Heparin	28 (15.9)	35 (19.8)
Rivaroxaban	27 (15.3)	34 (19.2)
Warfarin	64 (36.4)	59 (33.3)
Beta-blockers		
Metoprolol	59 (33.5)	59 (33.5)
Acids/electrolytes/glucose/vitamins		
Potassium	87 (49.4)	85 (48.0)
Sodium chloride	27 (15.3)	27 (15.3)
Cardiac therapy		
Amiodarone	55 (31.3)	54 (30.5)
Diuretics		
Bumetanide	27 (15.3)	26 (14.7)
Eplerenone	23 (13.1)	27 (15.3)
Furosemide	135 (76.7)	138 (78.0)
Metolazone	27 (15.3)	46 (26.0)
Spironolactone	77 (43.8)	81 (45.8)
Torasemide	65 (36.9)	69 (39.0)

Table 8: Concomitant therapies in the course of the study in ≥ 15 % of the patients in at least one study arm – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC (multipage table)

Study **Category of concomitant therapy** **Concomitant therapy[a]** **Drugs[a]**	**Tafamidis + BSC** **N[b] = 176**	**Placebo + BSC** **N[b] = 177**
Agents for acid-related diseases		
Omeprazole	29 (16.5)	31 (17.5)
Pantoprazole	38 (21.6)	53 (29.9)
Agents for constipation		
Docusate	17 (9.7)	33 (18.6)
Agents influencing lipid metabolism		
Atorvastatin	41 (23.3)	43 (24.3)
Simvastatin	32 (18.2)	39 (22.0)
Thyroid therapy		
Levothyroxine	43 (24.4)	34 (19.2)
Urologics		
Tamsulosin	30 (17.0)	36 (20.3)
Vaccines		
Influenza	24 (13.6)	29 (16.4)
Vitamins		
Colecalciferol	31 (17.6)	30 (16.9)
Multivitamins	35 (19.9)	35 (19.8)

a. Results taken from [5] without adjustments.
b. Number of randomized patients.
c. One drug may be assigned to several ATC classifications. To avoid duplications, one specific drug was only listed under one ATC at a time.

ATC: anatomical therapeutic chemical (classification system); BSC: best supportive care; MedDRA: Medical Dictionary for Regulatory Activities; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

Patients in the ATTR-ACT study were allowed to continue taking the drugs they had been taking at a stable dose for 4 weeks before the start of the study. Diuretics could still be adjusted during the first 4 weeks of the study. It was possible to start a new therapy after study start. Concomitant therapies using digitalis glycosides and calcium channel blockers were not allowed. No further requirements regarding treatment adjustments can be inferred from the study protocol [4].

The patients in the ATTR-ACT study received a variety of concomitant therapies during the course of the study. The data on concomitant therapy presented in Table 8 refer to the individual drugs; aggregated proportions related to drug classes are not available. Thus, double naming of patients is not excluded. There are no data prepared by the company on how many patients had their concomitant drug or non-drug therapy optimized during the course of the study.

There are no guidelines for the treatment of patients specifically with ATTR-CM. However, therapy recommendations for patients with amyloidosis and cardiac manifestation are available in various publications. In these publications, treatment of heart failure symptoms is considered a crucial part of therapy [15-17]. In principle, the same general therapy recommendations apply as for patients with cardiac failure. However, not all therapies used for conventional drug treatment of cardiac failure are also recommended in the treatment of adults with amyloidosis and cardiac manifestation. The therapy recommendations in the present therapeutic indication are primarily based on the use of diuretics [15-17]. It is pointed out that angiotensin converting enzyme (ACE) inhibitors or beta-receptor blockers are often ineffective for patients with ATTR-CM, are not well tolerated, or may lead to symptomatic hypotension [15,16,18,19]. Overall, there is a lack of evidence for the efficacy of these therapies in patients with ATTR-CM [16,17]. Treatment recommendations for arrhythmias include both drug and non-drug therapies (e.g. cardiac pacemaker implantation) [16,19,20].

It can be assumed that the patients in the ATTR-ACT study received concomitant treatment with a diuretic during the course of the study. This is inferred from the fact that, according to an inclusion criterion of the study, patients were included who had a history of cardiac failure that had required or required treatment with diuretics, as well as from the information on the diuretic agents used during the study (see Table 8). According to the available data, either none or at least less than 15% of the study population received an ACE inhibitor. At least 1 third of the study population took a beta-blocker during the course of the study. The company did not explain in Module 4 B to what extent treatment with beta-blockers was indicated in patients with ATTR-CM despite the treatment recommendations described above. It thus remains unclear for what reasons the patients took the beta-blockers. About 1 third of the patients took the antiarrhythmic drug amiodarone during the course of the study.

The concomitant therapies of digitalis glycosides and calcium channel blockers, which were prohibited under the study protocol, are not recommended due to potential toxicity from amyloid complexation [16-19,21]. This procedure corresponds to the therapy recommendations.

Overall, the present benefit assessment considers the concomitant therapy used in the ATTR-ACT study to be a sufficient implementation of the ACT BSC.

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Tafamidis + BSC** **N[a] = 176**	**Placebo + BSC** **N[a] = 177**
Study ATTR-ACT		
Age [years], mean (SD)	75 (7.2)	74 (6.7)
Sex [F/M], %	10/90	11/89
Smoking status, n (%)		
Non-smoker	93 (52.8)	104 (58.8)
Current smoker	7 (4.0)	7 (4.0)
Ex-smoker	72 (40.9)	62 (35.0)
Unspecified	4 (2.3)	4 (2.3)
Region, n (%)		
Europe	56 (31.8)	63 (35.6)
North America	109 (61.9)	108 (61.0)
Rest of the world	11 (6.3)	6 (3.4)
Family origin, n (%)		
Caucasian	136 (77.3)	146 (82.5)
Black	26 (14.8)	26 (14.7)
Asian	11 (6.3)	5 (2.8)
Other	3 (1.7)	0 (0)
Systolic blood pressure (mmHg), mean (SD)		
Supine	115.6 (16.0)	115.1 (15.7)
Standing	116.4 (16.3)	115.9 (15.9)
Diastolic blood pressure (mmHg), mean (SD)		
Supine	69.8 (10.3)	70.2 (9.5)
Standing	70.4 (10.3)	71.0 (10.3)
NT-proBNP level (pg/mL), median [min; max]	3122 [392; 22 020][b]	3161 [298; 16 787][b]
Disease duration: time between first diagnosis and randomization [years], mean (SD)	0.93 (1.18)	1.23 (1.44)
NYHA classification, n (%)		
Class I	16 (9.1)	13 (7.3)
Class II	105 (59.7)	101 (57.1)
Class III	55 (31.3)	63 (35.6)
Class IV	0 (0)	0 (0)
TTR genotype, n (%)		
Wild type TTR	134 (76.1)	134 (75.7)
Mutant TTR	42 (23.9)	43 (24.3)

Table 9: Characteristics of the study population – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Tafamidis + BSC** **N[a] = 176**	**Placebo + BSC** **N[a] = 177**
Accompanying diseases[c], n (%)	176 (100)	173 (97.7)
Cardiac disorders	151 (85.8)	150 (84.7)
Atrial fibrillation	93 (52.8)	89 (50.3)
Cardiac failure congestive	40 (22.7)	49 (27.7)
Coronary heart disease	35 (19.9)	40 (22.6)
Vascular disorders	104 (59.1)	107 (60.5)
Hypertension	90 (51.1)	84 (47.5)
Gastrointestinal disorders	68 (38.6)	75 (42.4)
Metabolism and nutrition disorders	122 (69.3)	113 (63.8)
Hyperlipidaemia	53 (30.1)	58 (32.8)
Renal and urinary disorders	55 (31.3)	68 (38.4)
Chronic kidney disease	31 (17.6)	41 (23.2)
Respiratory, thoracic and mediastinal disorders	83 (47.2)	78 (44.1)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n[d] (%)	38 (21.6)	54 (30.5)

a. Number of randomized patients.
b. The data come from the publication by Damy 2020 [6]. Since the values reported in Module 4 B are below 600 pg/mL (which was defined as inclusion criterion), an error in Module 4 B is assumed.
c. Relevant current accompanying diseases at baseline in ≥ 20 % of a treatment group. Coded according to MedDRA version 20.1; presentation of System Organ Classes and Preferred Terms; results taken from [5] without adjustments.
d. Patients who discontinued for reasons other than death.

BSC: best supportive care; F: female; M: male; max: maximum; MedDRA: Medical Dictionary for Regulatory Activities; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation; TTR: transthyretin; vs.: versus

The demographic and disease-specific characteristics of the patients were comparable between the treatment arms.

The mean age of the patient population of the study was 75 years, and most patients were male. Three quarters of the patients had wild type amyloidosis. About 2 thirds of the patients had NYHA class II cardiac failure and about 1 third NYHA class III cardiac failure. A small proportion (below 10%) of patients had NYHA class I cardiac failure. Patients with NYHA class IV cardiac failure were not included in the study.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ATTR-ACT	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the ATTR-ACT study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company described in Module 4 B that, according to German and international guidelines for the treatment of ATTR, the primary non-causal therapy option available is symptomatic standard care of cardiac failure. Accordingly, from the point of view of the company, it can be assumed that the patients received equivalent care within the centres.

The company also pointed out that the patient characteristics of the ATTR-ACT study population had been compared with the data of the retrospective cohort study ATTR-CM in Germany [22] based on the database of the Institute for applied healthcare research Berlin (InGef). This database contains data from the German health care context.

The company stated that the patient characteristics with regard to age and sex distribution are comparable between the ATTR-ACT study and the ATTR-CM study in Germany, and assumed that the results of the ATTR-ACT study can thus be transferred overall to the German healthcare context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity

- cardiovascular hospitalization
- endurance recorded with the 6 MWT
- health status recorded with the EQ-5D VAS

- Health-related quality of life
  - health-related quality of life recorded with the KCCQ OSS
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study	Outcomes							
	All-cause mortality	Cardiovascular hospitalization[a]	Endurance (6 MWT)	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs[b]	Discontinuation due to AEs[b]	Dyspnoea (PT, AE)
ATTR-ACT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Hospitalization is defined as a non-elective hospital stay of at least 24 hours or – if the exact time of admission and discharge is not available – in case of a date change. Cardiovascular hospitalization was recorded based on the frequency of hospitalizations due to a cardiovascular event (cardiac failure, arrhythmia, myocardial infarction, stroke, and other cardiovascular events). The outcome was adjudicated by an independent committee (Endpoint Adjudication Committee, EAC). In case of doubt, the event was classified as cardiovascular if there was an indication of a cardiovascular cause, even if the information was ambiguous.

b. Without events of the SOC "cardiac disorders".

AE: adverse event; BSC: best supportive care; EAC: Endpoint Adjudication Committee; EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test

Note on cardiovascular hospitalization

For the outcome "cardiovascular hospitalization", the present benefit assessment considers both the number of patients with event and the frequency of events (rate), as it is relevant for the benefit assessment in the present therapeutic indication to consider both the prevention of cardiovascular hospitalizations and the reduction of the rate of these hospitalizations.

In the ATTR-ACT study, an independent Endpoint Adjudication Committee (EAC) assessed whether a death or hospitalization were cardiovascular-related. An EAC charter defined which events were rated as cardiovascular. There are 5 versions of the EAC charters in total, which came into force between 27 November 2013 and 17 September 2016. Among other things, these versions included changes of the definitions of cardiovascular-related death, as well as hospitalization due to cardiac failure and, in a later change, due to other cardiovascular events.

For the outcome of cardiovascular mortality, the company described in Module 4 B that the changes of the definitions in the EAC charters had either occurred before the first case assessment or had no influence on the assessment of the event as cardiovascular or non-cardiovascular, and thus did not influence the outcome of cardiovascular mortality. The company did not state whether or what significance the changes had for the recording and the results of the outcome "cardiovascular hospitalizations".

Note on responder analyses on the outcome of health-related quality of life

For the outcome of health-related quality of life, recorded with the KCCQ OSS instrument, the company presented responder analyses for the time to deterioration by ≥ 5 points in its dossier.

These were not used for the dossier assessment. As explained in the General Methods of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range).

In the present assessment, the continuous analyses are used for the benefit assessment for the KCCQ OSS due to the lack of suitable responder analyses.

The responder analyses presented by the company for the time to deterioration by ≥ 5 points are presented in Appendix C of the full dossier assessment.

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study	Study level	Outcomes							
		All-cause mortality	Cardiovascular hospitalization	Endurance (6 MWT)	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs[a]	Discontinuation due to AEs[a]	Dyspnoea (PT, AE)
ATTR-ACT	L	L	H[b]	H[c]	L	L	L	L	L

a. Without events of the SOC "cardiac disorders".
b. Unclear influence of changes in the definitions of hospitalization due to cardiac failure, and in a later change due to other cardiovascular events, made during the course of the study.
c. High proportion of patients with missing values at month 30 or large difference in missing values between the treatment groups (21% tafamidis + BSC vs. 35% placebo +BSC).

AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test

The risk of bias was rated as low for the results of the following outcomes: all-cause mortality, health status, health-related quality of life, SAEs, discontinuation due to AEs, and dyspnoea. This concurs with the company's assessment.

The risk of bias of the results of the outcome "cardiovascular hospitalization" was rated as high. This was due to an unclear influence of the changes in the definitions of hospitalization due to cardiac failure, and in a later change due to other cardiovascular events, made during the course of the study. The company presented this outcome as supplementary information and without assessment of the risk of bias.

Deviating from the company, the risk of bias of the outcome "endurance" was assessed as high. This was due to a high proportion of patients with missing values at month 30 or a large difference in missing values between the study arms (21% tafamidis + BSC vs. 35% placebo +BSC). The company assessed the risk of bias for the results of the outcome "endurance" as low.

2.4.3 **Results**

Table 13 to Table 16 summarize the results on the comparison of tafamidis + BSC with placebo + BSC in patients with wild type or hereditary ATTR-CM. Where necessary, calculations by the Institute are provided in addition to the data from the company's dossier.

If available, Kaplan-Meier curves on the event time analyses of the outcomes included are presented in Appendix A of the full dossier assessment.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix B of the full dossier assessment.

Table 13: Results (mortality, time to event) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome category	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. placebo + BSC
Outcome	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI]; p-value[a]**
ATTR-ACT					
Mortality					
All-cause mortality[b]	176	NA 49 (27.8)	177	NA 72 (40.7)	0.65 [0.45; 0.93]; 0.020
Cardiovascular mortality[b] (supplementary information)	176	NA 40 (22.7)	177	NA 59 (33.3)	0.64 [0.43; 0.96]; 0.029

a. HR, CI and p-value: Cox proportional hazards model adjusted for NYHA classification and TTR genotype.
b. Patients who discontinued the study for heart transplantation, combined heart and liver transplantation, or a cardiac mechanical assist device, are included in the analysis with their actual vital status (second sensitivity analysis of the company). This means that the time of the study discontinuation is not taken into account as an event (death) in the analysis (as was done in the decisive analysis of the company) or is not rated as censoring.

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NYHA: New York Heart Association; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus

Table 14: Results (morbidity, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome category Outcome	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. placebo + BSC
	N	Rate [95% CI][a]	N	Rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
ATTR-ACT					
Morbidity					
Cardiovascular hospitalization	176	0.49 [0.42; 0.57]	177	0.70 [0.62; 0.80]	0.70 [0.57; 0.85]; < 0.001

a. Mean rates with CI (per treatment group) as well as rate ratio with CI and p-value (group comparison): Poisson regression with the variables treatment, TTR genotype, NYHA classification and the interaction terms between treatment and TTR genotype as well as between treatment and NYHA classification; according to the company, adjusted for the observation period with treatment. It remains unclear whether this is the observation or treatment period.

BSC: best supportive care; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus

Table 15: Results (morbidity, side effects, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome category Outcome	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ATTR-ACT					
Morbidity					
Cardiovascular hospitalization	176	96 (54.5)	177	107 (60.5)	0.90 [0.75; 1.08]; 0.287
Side effects					
AEs[b] (supplementary information)	176	170 (96.6)	177	173 (97.7)	-
SAEs[b]	176	106 (60.2)	177	102 (57.6)	1.05 [0.88; 1.24]; 0.683
Discontinuation due to AEs[b]	176	20 (11.4)	177	28 (15.8)	0.72 [0.42; 1.23]; 0.247
Dyspnoea (PT, AE)	176	29 (16.5)	177	55 (31.1)	0.52 [0.35; 0.77]; 0.001[c]

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]).
b. Without events of the SOC "cardiac disorders".
c. RR, CI and p-value: generalized linear model adjusted for TTR genotype and NYHA classification.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TTR: transthyretin; vs.: versus

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome category Outcome	Tafamidis + BSC			Placebo + BSC			Tafamidis + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at month 30 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at month 30 mean (SE)[b]	MD [95% CI]; p-value[b]
ATTR-ACT							
Morbidity							
Endurance (6 MWT)[c]	158	344.78 (120.28)	−54.77 (7.46)	152	353.26 (125.98)	−130.54 (9.80)	75.77 [55.99; 95.55]; < 0.001
Health status (EQ-5D VAS)[c]	160	68.27 (18.36)	−3.43 (1.40)	160	66.48 (17.76)	−12.92 (1.62)	9.49 [6.05; 12.94]; < 0.001 Hedges' g: 0.60 [0.38; 0.83][d]
Health-related quality of life							
KCCQ OSS[c]	163	67.12 (21.29)	−7.34 (1.50)	160	65.9 (21.74)	−20.82 (1.98)	13.48 [9.16; 17.80]; < 0.001 Hedges' g: 0.50 [0.28; 0.73][d]
Domains (supplementary information)							
Physical limitation	161	69.21 (22.70)	−10.76 (1.65)	159	68.24 (24.18)	−22.61 (2.21)	11.86 [7.62; 16.09]
Symptoms[e]	163	72.82 (20.49)	−5.44 (1.45)	160	72.1 (20.64)	−18.75 (2.32)	13.31 [8.46; 18.15]
Social limitation	158	63.64 (28.58)	−8.71 (2.35)	152	63.1 (28.97)	−24.70 (2.30)	15.98 [10.35; 21.62]
Quality of life	163	62.07 (25.08)	−1.52 (1.82)	160	59.98 (24.65)	−15.96 (2.38)	14.44 [9.61; 19.28]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Mean and SE (change at month 30 per treatment arm) and MD, CI and p-value (group comparison): MMRM analysis with the variables treatment, visit, baseline value, TTR genotype, and the interaction term between treatment and visit.
c. Higher (increasing) values indicate improved symptoms/health-related quality of life; positive effects ([tafamidis + BSC] minus [placebo + BSC]) indicate an advantage for tafamidis + BSC.
d. Institute's calculation based on the MD and CI of the MMRM.
e. Symptom burden and symptom frequency.

BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference, MMRM: mixed-effects model with repeated measures; N: number of analysed patients; OSS: overall summary score; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test

Due to the fact that the tafamidis formulation in the ATTR-ACT study deviates from the SPC, the certainty of conclusions was downgraded (see Section 2.3.2). Based on the available data, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

Mortality

All-cause mortality

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "all-cause mortality". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of another operationalization.

Morbidity

Cardiovascular hospitalization

For the outcome "cardiovascular hospitalization", there was a statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC for the total population based on the rate, but not based on the proportion of patients with (at least one) event. However, there was an effect modification by the characteristic "NYHA classification" for both operationalizations. For patients with NYHA class I + II cardiac failure, this resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for the outcome "cardiovascular hospitalization". For patients with NYHA class III cardiac failure, in contrast, there was a hint of lesser benefit of tafamidis + BSC in comparison with BSC for this outcome (see Section 2.4.4).

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of the total population on the basis of the outcome "total hospitalization".

Endurance (recorded with the 6 MWT)

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "endurance". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Health status (recorded with the EQ-5D VAS)

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "health status". The SMD in the form of Hedges' g was considered to assess the relevance of the result. The 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. There was an effect modification by the characteristic "TTR genotype". However, the results in the 2 subgroups did not differ in the direction of effect and in the extent from the result of the total study population (see Section 2.4.4), so that the characteristic was not considered further for the outcome "health status". This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Health-related quality of life

Health-related quality of life (recorded with the KCCQ OSS)

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "health-related quality of life". The SMD in the form of Hedges' g was considered to assess the relevance of the result. The 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of the responder analysis "time to deterioration by ≥ 5 points" and no added benefit on the basis of the responder analysis "time to improvement by ≥ 5 points".

Side effects

Overall rates of SAEs and discontinuation due to AEs

Operationalization

Analyses excluding all events of the System Organ Class (SOC) "cardiac disorders" were available for the outcomes "SAEs" and "discontinuation due to AEs".

Results

There was no statistically significant difference between the treatment groups for the outcome "SAEs" or for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from tafamidis + BSC in comparison with BSC for either of these outcomes; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the operationalization used by the company and using event time analyses.

Dyspnoea (PT, AE)

A statistically significant difference in favour of tafamidis + BSC in comparison with placebo + BSC was shown for the outcome "dyspnoea". However, there was an effect modification by the characteristic "NYHA classification". For patients with NYHA class I + II cardiac failure, this resulted in a hint of lesser harm of tafamidis + BSC in comparison with BSC for the outcome "dyspnoea". For patients with NYHA class III cardiac failure, in contrast, there was no hint of greater or lesser harm of tafamidis + BSC in comparison with BSC for this outcome; greater or lesser harm for this patient group is therefore not proven (see Section 2.4.4).

It is questionable whether the effect for the outcome "dyspnoea" (PT, AE) actually is to be assigned to the outcome category "side effects" or whether it rather reflects the clinical picture of the underlying disease.

The assessment of the outcome "dyspnoea" deviates from the approach of the company, which used the PT dyspnoea on the basis of event time analyses, but, together with further AEs, derived an indication of lesser harm of tafamidis compared with the comparator therapy.

2.4.4 **Subgroups and other effect modifiers**

The following subgroups were used for the present assessment:

- sex (female/male)
- NYHA classification (NYHA class I + II/NYHA class III)
- TTR genotype (wild type TTR/mutant TTR)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes of cardiovascular hospitalization, endurance, health status and dyspnoea (PT, AE) used in the present benefit assessment, subgroup analyses were available for each of the potential effect modifiers mentioned above.

For the outcomes of all-cause mortality, health-related quality of life and the overall rates of SAEs and discontinuation due to AEs, subgroup analyses were available in Module 4 B, but not for the operationalizations used for these outcomes in the present benefit assessment.

Table 17, Table 18 and Table 19 present the subgroup results on the comparison of tafamidis + BSC with placebo + BSC.

Table 17: Subgroups (morbidity, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome Characteristic Subgroup	Tafamidis + BSC		Placebo + BSC		Tafamidis + BSC vs. placebo + BSC	
	N	Rate [95% CI][a]	N	Rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]	p-value[a]
ATTR-ACT						
Cardiovascular hospitalizations						
NYHA classification						
NYHA class I or II	121	0.35 [0.29; 0.43]	114	0.71 [0.61; 0.83]	0.49 [0.38; 0.64]	< 0.001
NYHA class III	55	0.99 [0.80; 1.21]	63	0.68 [0.53; 0.86]	1.46 [1.07; 2.00]	0.018
Total					Interaction:	< 0.001[b]

a. Mean rates with CI (per treatment group) as well as rate ratio with CI and p-value (group comparison): Poisson regression with the variables treatment, TTR genotype, and the interaction term between treatment and TTR genotype, adjusted for the treatment period.
b. Poisson regression with corresponding interaction term.

BSC: best supportive care; CI: confidence interval; N: number of analysed patients; NYHA: New York Heart Association; RCT: randomized controlled trial; TTR: transthyretin; vs.: versus

Table 18: Subgroups (morbidity, side effects, dichotomous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome Characteristic Subgroup	Tafamidis + BSC N	Tafamidis + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients with event n (%)	Tafamidis + BSC vs. placebo + BSC RR [95% CI][a]	Tafamidis + BSC vs. placebo + BSC p-value[a]
ATTR-ACT						
Cardiovascular hospitalizations						
NYHA classification						
NYHA class I or II	121	53 (43.8)	114	70 (61.4)	0.71 [0.56; 0.91]	0.007
NYHA class III	55	43 (78.2)	63	37 (58.7)	1.33 [1.04; 1.71]	0.027
Total					Interaction:	< 0.001[b]
Dyspnoea (PT, AE)						
NYHA classification						
NYHA class I or II	121	17 (14.0)	114	40 (35.1)	0.39 [0.24; 0.65][c]	< 0.001[c]
NYHA class III	55	12 (21.8)	63	15 (23.8)	0.94 [0.49; 1.83][c]	0.865[c]
Total					Interaction:	0.037[b]

a. Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]).
b. Institute’s calculation, Cochran’s Q test.
c. Generalized linear model adjusted for TTR genotype.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; TTR: transthyretin; vs.: versus

Table 19: Subgroups (morbidity, continuous) – RCT, direct comparison: tafamidis + BSC vs. placebo + BSC

Study Outcome	Tafamidis + BSC			Placebo + BSC			Tafamidis + BSC vs. placebo + BSC
Characteristic Subgroup	N[a]	Values at baseline mean (SD)	Change at month 30 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at month 30 mean (SE)[b]	MD [95% CI]; p-value[b]
ATTR-ACT							
Health status (EQ-5D VAS)[c]							
TTR genotype							
Mutant TTR	37	67.29 (18.97)	−0.29 (2.75)	36	69.33 (17.92)	−25.89 (5.21)	25.59 [13.60; 37.59]; < 0.001 Hedges' g: 0.97 [0.48; 1.45][d]
Wild type TTR	123	68.59 (18.23)	−3.63 (1.26)	124	65.57 (17.68)	−10.68 (1.91)	7.05 [3.42; 10.68]; < 0.001 Hedges' g: 0.48 [0.23; 0.74][d]
Total						Interaction:	p-value = 0.004[e]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Mean and SE (change at month 30 per treatment arm) and MD, CI and p-value (group comparison): MMRM analysis with the variables treatment, visit, baseline value, visit, and the interaction term treatment and visit.
d. Higher (increasing) values indicate better health status; positive effects ([tafamidis+ BSC] minus [placebo + BSC]) indicate an advantage for tafamidis + BSC.
d. Institute's calculation based on the MD and CI of the MMRM.
e. Cochran's Q test.

BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference, MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; TTR: transthyretin; VAS: visual analogue scale; vs.: versus

Morbidity

Cardiovascular hospitalization

For the outcome "cardiovascular hospitalization", there was an effect modification by the characteristic of NYHA classification, both on the basis of the rate and on the basis of the proportion of patients with (at least one) event. For the subgroup of NYHA class I + II, there was a statistically significant difference in favour of tafamidis + BSC versus placebo + BSC for both operationalizations. For patients with NYHA class I + II cardiac failure, this resulted in a hint of an added benefit of tafamidis + BSC in comparison with BSC for this outcome. For the subgroup of NYHA class III, there was a statistically significant difference to the disadvantage of tafamidis + BSC versus placebo + BSC for both operationalizations. For patients with NYHA class III cardiac failure, this resulted in a hint of lesser benefit of tafamidis + BSC in comparison with BSC for this outcome.

The company did not consider the subgroups for cardiovascular hospitalization.

Health status (recorded with the EQ-5D VAS)

There was an effect modification by the characteristic of TTR genotype for the outcome "health status". For both subgroups, the changes at month 30 averaged over the course of the study showed statistically significant differences in favour of tafamidis + BSC in comparison with placebo + BSC. In each case, the 95% CI of the SMD was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect in each case. This and also the extent for both subgroups concurred with the result of the total study population. Therefore, the characteristic of TTR genotype was not considered further for the outcome "health status".

This deviates from the approach of the company in that this effect is only clinically relevant in the subgroup with mutant TTR. Concurring with this assessment, the company considered the effect modification by the characteristic of TTR genotype as not relevant to the conclusion.

Side effects

Dyspnoea (AE)

There was an effect modification by the characteristic of NYHA classification for the outcome "dyspnoea". For the subgroup of NYHA class I + II, there was a statistically significant difference in favour of tafamidis + BSC versus placebo + BSC. For patients with NYHA class I + II cardiac failure, this resulted in a hint of lesser harm of tafamidis + BSC in comparison with BSC for this outcome. In contrast, there was no statistically significant difference between the treatment groups for the NYHA class III subgroup. This resulted in no hint of lesser or greater harm for this outcome. Greater or lesser harm is therefore not proven for these patients.

This concurs with the result of the company insofar as the company described the same effects for the subgroups. However, it considered the effect modification for the outcome "dyspnoea" as not relevant to the conclusion and instead derived an indication of an added benefit of tafamidis based on the SOC respiratory, thoracic and mediastinal disorders, and using event time analyses for the total population.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 20).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Dyspnoea

Based on the available data, it cannot be assumed that the events included in the outcome "dyspnoea" are rather serious/severe. The outcome was therefore allocated to non-serious/non-severe outcomes.

Table 20: Extent of added benefit at outcome level: tafamidis + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tafamidis + BSC vs. placebo + BSC** **Median time to event (months) or rate or mean change at month 30 or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Median: NA vs. NA HR: 0.65 [0.45; 0.93]; p = 0.020 probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Cardiovascular hospitalization		
NYHA class I or II	Rate: 0.35 vs. 0.71 rate ratio: 0.49 [0.38; 0.64]; p < 0.001 proportions of events: 43.8 % vs. 61.4 % RR: 0.71 [0.56; 0.91] p = 0.007 probability: "hint"	Outcome category: serious/severe symptoms/late complications rate ratio: $CI_u < 0.75$, risk ≥ 5% RR: $0.90 \leq CI_u < 1.00$ added benefit, extent: "considerable"[c]
NYHA class III	Rate: 0.99 vs. 0.68 rate ratio: 1.46 [1.07; 2.00] rate ratio: 0.68 [0.50; 0.93][d] p = 0.018 proportions of events: 78.2 % vs. 58.7 % RR: 1.33 [1.04; 1.71] RR: 0.75 [0.58; 0.96][d] p = 0.027 probability: "hint"	Outcome category: serious/severe symptoms/late complications rate ratio: $0.90 \leq CI_u < 1.00$ RR: $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"[e]
Endurance (6 MWT)	Mean change: −54.77 vs. −130.54 MD: 75.77 [55.99; 95.55]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health status (EQ-5D VAS)	Mean change: −3.43 vs. −12.92 MD: 9.49 [6.05; 12.94] p < 0.001 Hedges' g: 0.60 [0.38; 0.83][f] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"

Table 20: Extent of added benefit at outcome level: tafamidis + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tafamidis + BSC vs. placebo + BSC** **Median time to event (months) or rate or mean change at month 30 or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
Health-related quality of life (KCCQ OSS)	Mean change: −7.34 vs. −20.82 MD: 13.48 [9.16; 17.80]; p < 0.001 Hedges' g: 0.50 [0.28; 0.73][f] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Side effects		
SAEs	Proportions of events: 60.2 % vs. 57.6 % RR: 1.05 [0.88; 1.24] p = 0.683	Greater/lesser harm not proven
Discontinuation due to AEs	Proportions of events: 11.4 % vs. 15.8 % RR: 0.72 [0.42; 1.23] p = 0.247	Greater/lesser harm not proven
Dyspnoea (PT, AE) NYHA classification		
NYHA class I or II	Proportions of events: 14.0 % vs. 35.1 % RR: 0.39 [0.24; 0.65]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
NYHA class III	Proportions of events: 21.8 % vs. 23.8 % RR: 0.94 [0.49; 1.83]; p = 0.865	Outcome category: non-serious/non-severe side effects greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The assessment of the extent as "considerable" results from the joint consideration of the results on the rate ratio (extent "major") and the proportion of patients with event (extent "minor").
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The assessment of the extent as "minor" results from the joint consideration of the results on the rate ratio (extent "minor") and the proportion of patients with event (extent "minor").
f. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred.

Table 20: Extent of added benefit at outcome level: tafamidis + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tafamidis + BSC vs. placebo + BSC** **Median time to event (months) or rate or mean change at month 30 or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; NYHA: New York Heart Association; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test		

2.5.2 Overall conclusion on added benefit

Table 21 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of tafamidis + BSC compared with BSC

Positive effects	**Negative effects**
Mortality ▪ All-cause mortality[a]: hint of an added benefit – extent "considerable"	–
Serious/severe symptoms/late complications ▪ Cardiovascular hospitalization: ▫ NYHA class I + II: hint of an added benefit – extent: "considerable"	Serious/severe symptoms/late complications ▪ Cardiovascular hospitalization: ▫ NYHA class III: hint of lesser benefit – extent: "minor"
Non-serious/non-severe symptoms/late complications ▪ Endurance (6 MWT): hint of an added benefit – extent: "non-quantifiable" ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: "non-quantifiable"	–
Health-related quality of life ▪ Health-related quality of life (KCCQ OSS)[a]: hint of an added benefit – extent "non-quantifiable"	–
Non-serious/non-severe side effects: ▪ Dyspnoea (PT, AE) ▫ NYHA class I + II: hint of an added benefit – extent: "considerable"	–
a. For the operationalization of this outcome used in the benefit assessment, no subgroup analyses for the characteristic of NYHA classification were prepared for the dossier. AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; OSS overall summary score; PT: Preferred Term; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus; 6 MWT: 6-minute walking test	

The overall picture shows both positive and negative effects of tafamidis + BSC in comparison with BSC, which are partly dependent on the characteristic of NYHA classification. For this reason, the positive and negative effects are assessed below separately for patients with NYHA class I + II cardiac failure and for patients with NYHA class III cardiac failure.

Patients with NYHA class I + II cardiac failure at baseline

There were only positive effects for patients with NYHA class I + II cardiac failure at baseline. These include effects of considerable extent (outcomes "all-cause mortality", "cardiovascular hospitalization" and "dyspnoea") and effects on several outcomes of non-quantifiable extent each. For the outcome "dyspnoea", however, it is questionable whether the effect for this outcome can actually be assigned to the outcome category of side effects or whether it does not rather reflect the clinical picture of the underlying disease.

In summary, there is a hint of considerable added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class I + II cardiac failure at baseline.

Patients with NYHA class III cardiac failure at baseline

There were both positive and negative effects for patients with NYHA class III cardiac failure at baseline. There was an advantage of considerable extent in all-cause mortality. There were further positive effects, each with a non-quantifiable added benefit, in the outcomes "endurance", "health status", and "health-related quality of life". However, these were accompanied by lesser benefit of minor extent in the outcome "cardiovascular hospitalization".

For the 2 outcomes "all-cause mortality" and "health-related quality of life" in particular, no subgroup analyses were prepared by the company for the operationalizations used in the benefit assessment. Considering the negative effect for the outcome "cardiovascular hospitalization" and the fact that subgroup analyses for the characteristic of NYHA classification were not available for all outcomes, it cannot be assessed whether there is any advantage at all or even lesser benefit for these outcomes in patients with NYHA class III cardiac failure.

In summary, there is no hint of an added benefit of tafamidis + BSC in comparison with BSC for patients with ATTR-CM and with NYHA class III cardiac failure at baseline.

The result of the assessment of the added benefit of tafamidis in comparison with the ACT is summarized in Table 22.

Table 22: Tafamidis – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients	Best supportive care[b, c, d]	▪ Patients with NYHA class I + II cardiac failure: hint of considerable added benefit ▪ Patients with NYHA class III cardiac failure: added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation corresponding to the state of medical knowledge is carried out in the study arms, taking into account the special features of the disease hATTR amyloidosis, and is documented as concomitant treatment.
d. It is assumed that liver transplantation is not an option at the time of therapy with tafamidis.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloid cardiomyopathy; G-BA: Federal Joint Committee; hATTR: hereditary transthyretin amyloidosis; NYHA: New York Heart Association

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for the total population.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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