IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A11-31

Tafamidis meglumine –

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

Extract

[1] Translated extract of Sections 2.1 to 2.6 of the German-language dossier assessment ("Tafamidis Meglumin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 13.03.2012). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the "full dossier assessment"). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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List of tables[3]

[3] Table numbers in this extract start with "2", as numbers follow the numbering in the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NIS-LL	Neuropathy Impairment Score in the Lower Limbs
NSAID	non-steroidal anti-inflammatory drugs
QOL-DN	(Norfolk) Quality of Life – Diabetic Neuropathy (Score)
RCT	randomized controlled trial
SF-36	Short Form 36
SGB	Sozialgesetzbuch (Social Code Book)
TTR-FAP	transthyretin familial amyloid polyneuropathy
Val30Met	mutation at Position 30 of the aminoacid sequence of the transthyretin gene leads to a replacement of the aminoacid valine by methionine

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 14.12.2011, 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 meglumine. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The aim of this report is to assess tafamidis meglumine (tafamidis) compared to best supportive care (BSC) in adult patients with transthyretin amyloidosis with stage 1 symptomatic polyneuropathy.

For this benefit assessment it was possible to take account of studies that compared tafamidis as monotherapy or in combination with BSC, with treatment consisting of BSC alone. The assessment was carried out through the comparison, undertaken in the included study, of tafamidis in combination with BSC (tafamidis/BSC) with a treatment consisting of BSC alone (placebo/BSC). The assessment was undertaken based on patient-relevant outcomes. Both randomized controlled trials (RCTs) with a direct comparator as well as other investigations were included in the assessment.

Results

Two relevant studies (Fx-005, Fx1A-201) were available for the assessment. The study Fx-005 was a double-blind RCT, in which tafamidis in combination with BSC was compared with placebo in combination with BSC. The Fx1A-201 study was an open-label, non-controlled study in which tafamidis was given in combination with BSC.

The design of the studies precluded a pooling of their results into meta-analyses. Due to the quality of the studies, their informative value differs. In addition, the patient populations of the 2 studies differed with respect to the mutation of the transthyretin (TTR) gene. The RCT Fx-005 investigated exclusively patients with a Val30Met mutation, whereas in the non-controlled study Fx1A-201, patients with a non-Val30Met mutation were enrolled (a non-Val30Met mutation is present in approx. 15% of TTR familial amyloid polyneuropathy (TTR-FAP) patients worldwide). Transferability of the results of the RCT to the non-Val30Met population is possible to a limited extent (the same direction of effect can probably be assumed in the case of positive effects), but the transferability of results concerning harm remains unclear. Therefore the results on these subpopulations are shown separately according to genotype.

The following results were shown.

Mortality

The RCT Fx-005 in patients with Val30Met mutation showed no statistically significant difference between tafamidis/BSC and placebo/BSC. No deaths occurred in the non-controlled study Fx1A-201 in patients with a non-Val30Met mutation. An added benefit of tafamidis in combination with BSC compared to BSC alone cannot be derived for all-cause mortality.

Morbidity

Neurological impairment (NIS-LL response)

The neurological impairment of patients was measured with the Neuropathy Impairment Score in the Lower Limbs (NIS-LL) scale. The proportion of patients who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher in the RCT Fx-005 (patients with Val30Met mutation) under tafamidis/BSC than under placebo/BSC. Depending on the imputation method for missing values, the difference was statistically significant in one analysis, but not in another. Overall, the result is assessed as a hint[4] of a positive effect of tafamidis in combination with BSC compared to BSC alone in the population of patients with Val30Met mutation. Neurological impairment in the study population was not particularly pronounced; the measured impairment in the lower region of the NIS-LL scale cannot be classed as severe symptoms. Due to the marginal effect size for non-severe symptoms, no added benefit is derived for the outcome "neurological impairment".

It is assumed that the direction of effect observed in the RCT for the outcome "neurological impairment" can be applied to the non-Val30Met population, but the size of the effect remains unclear. For patients with non-Val30Met mutation, there is a hint of a positive effect of tafamidis in combination with BSC for this outcome. Whether the effect is large enough to show an added benefit for patients with non-Val30Met mutation with regard to neurological impairment remains unclear.

Health-related quality of life

Health-related quality of life was recorded in both included studies with the Norfolk Quality of Life – Diabetic Neuropathy Score (QOL-DN). The Fx1A-201 study also recorded health-related quality of life with the Short Form 36 (SF-36) questionnaire. The RCT Fx-005 showed no statistically significant difference between tafamidis/BSC and placebo/BSC for the QOL-

[4]On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit of an intervention. 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 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 data not interpretable), see [1]. The extent of added benefit is graded into 6 categories: (1) major, (2) considerable, (3) minor, (4) non-quantifiable, (5) no added benefit, or (6) less benefit, see [2].

DN. No conclusion regarding the effect of tafamidis on health-related quality of life is possible based on the data of the SF-36 from the non-controlled Fx1A-201 study alone. Overall, an added benefit of tafamidis in combination with BSC compared to BSC alone cannot be derived for health-related quality of life.

Adverse events

In the RCT Fx-005 in patients with Val30Met mutation, comparison of the overall rate of adverse events, the overall rate of serious adverse events, the overall rate of treatment discontinuations due to adverse events, and the overall rates of gastrointestinal events and infections showed no statistically significant difference between the treatment groups. Hence, in the Val30Met population, no lesser or greater harm from tafamidis in combination with BSC compared to BSC alone can be derived for the above-named outcomes. No conclusions regarding adverse events of tafamidis can be derived from the non-controlled Fx1A-201 study in patients with non-Val30Met mutation.

Overall conclusion on added benefit

The overall conclusion on added benefit is given by the legal basis for the assessment of drugs for the treatment of rare (orphan) diseases.

In accordance with § 35a SGB V, an added benefit of drugs for the treatment of rare diseases (orphan drugs) is deemed as proven by the fact that they have been approved. The decision on the extent of added benefit is made by the G-BA.

2.2 Research question

Tafamidis is an orphan drug. In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved. However, evidence must be presented regarding groups of patients for whom a therapeutically important added benefit exists. In addition, the extent of the added benefit of tafamidis must be assessed.

The company followed the specification of the G-BA and chose BSC as appropriate comparator therapy for the assessment in its dossier.

The aim of this report is to assess tafamidis compared to BSC in adult patients with transthyretin amyloidosis with stage 1 symptomatic polyneuropathy.

The assessment was undertaken based on patient-relevant outcomes. RCTs with a direct comparator as well as other investigations (non-controlled studies) were included.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

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

- Studies on tafamidis completed by the company up to 17.11.2011 (study list of the company)
- Results of a search for studies on tafamidis in trial registries (last search 17.11.2011, searches by the company)
- The Institute's own search for studies on tafamidis in trial registries on 05.01.2012 to check the company's search results. The check produced no deviations from the study pool presented in the company's dossier.

The identified studies corresponded to the study pool of the company. However, not all studies were included in the assessment, because not all of them produced the best available evidence to answer the research question.

Further information about the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 2: Study pool – studies with tafamidis

Therapeutic indication Study	Study category		
	Pivotal study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Randomized controlled trial			
Fx-005	yes	yes	no
Other investigations: non-controlled study			
Fx1A-201	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

The study pool of RCTs with the drug to be evaluated for the benefit assessment corresponded to the company's study pool of RCTs. The study pool of other investigations deviated from the company's study pool in that the Fx-006 study was not taken into account. The non-controlled extension study Fx-006 was excluded from the assessment because an RCT (Fx-005) was available for the subpopulation investigated (patients with TTR-FAP with Val30Met mutation). Hence, no added information for the assessment of tafamidis was to be expected from the non-controlled extension study (see Section 2.7.2.7 of the full dossier assessment).

Section 2.6 contains a list of data sources cited by the company for the studies included.

Further information about the results of information retrieval and resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Section 2.7.2.3 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the design of the studies included in the benefit assessment. The first study (Fx-005) is a double-blind, randomized, placebo-controlled trial in which adult patients diagnosed with TTR-FAP were treated with tafamidis + BSC or with placebo + BSC. Only patients with a Val30Met mutation of the TTR gene were enrolled in this study (this mutation leads to a replacement of the aminoacid valine by methionine at Position 30 of the aminoacid sequence of the transthyretin gene).

The second study (Fx1A-201) is a non-controlled study in which adult patients diagnosed with FAP were treated with tafamidis. In this study, exclusively patients with a mutation different to the Val30Met mutation of the TTR gene (non-Val30Met) were enrolled.

The company derives conclusions on the added benefit of tafamidis in the entire population of patients with TTR-FAP primarily from the RCT and supports these conclusions by adding the results from the non-controlled study for patients with non-Val30Met mutation.

Patients with Val30Met mutation differ from patients with other, non-Val30Met mutations as follows:

- The Val30Met mutation is more common than the non-Val30Met mutation. In addition, the frequency of the individual genotypes in endemic and non-endemic regions is very different [3].
- The various genotypes lead to a difference in severity of the disease (differences in the deposition of amyloid in certain tissues [e.g. heart and central nervous system], in the age of onset, in the duration of the disease at diagnosis and in the time course of the symptoms).

These differences raise the question as to how far the results from the RCT in patients with Val30Met mutation can be transferred to patients with non-Val30Met mutation.

Based on the documents in the dossier, the Institute can agree with the company to the extent that possible positive effects of tafamidis in the patient populations with Val30Met mutation are in the same direction in the population with non-Val30Met mutation. However, in the Institute's view, no conclusions can be drawn from the results in the Val30Met subpopulation regarding the size of the positive effects in the non-Val30Met subpopulation. As regards negative effects, based on the results for patients withVal30Met mutation, no conclusions are possible either on the direction or size of the effect in patients with non-Val30Met mutation (for detailed reasoning, see Section 2.7.2.7 of the full dossier assessment). The two subpopulations are therefore considered separately.

In the RCT Fx-005, patients were randomly allocated to treatment with tafamidis or placebo. In addition, both groups could be given concomitant medication. Only the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) was limited to some extent, but at the same

time this restriction did not exist for all NSAIDs (see Table 4). This treatment regimen is regarded as sufficiently comprehensive and suited to patient needs to qualify as BSC.

Table 3: Characteristics of the included studies

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
Randomized controlled trial						
Fx-005	RCT, placebo controlled, double-blind, parallel, multicentre	Patients (without liver transplantation) with TTR-FAP with Val30Met mutation and positive biopsy	Tafamidis 20 mg once daily (N = 65) Placebo (N = 63) In each case + BSC	18 months	Argentina, Brazil, Germany, France, Portugal, Sweden, Spain, UK, USA Period 01/2007-05/2009	Primary: response (NIS-LL), health-related quality of life (Norfolk QOL-DN) Secondary: neurological impairment (NIS-LL), adverse events
Other investigations: non-controlled study						
Fx1A-201	Non-controlled, open-label, multicentre	Patients with TTR-FAP with non-Val30Met mutation	Tafamidis 20 mg once daily (N = 21) + BSC	12 months	Germany, France, Italy, USA Period 06/2008-01/2010	Primary: TTR stabilization in Week 6, compared with baseline value Secondary: neurological impairment (NIS-LL), health-related quality of life (Norfolk QOL-DN, SF-36), adverse events

a: Extracted primary outcome criteria contain information with no consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain only information about available outcomes of relevance for this benefit assessment.

BSC: best supportive care; N: number of randomized patients; NIS-LL: Neuropathy Impairment Score in the Lower Limbs; QOL-DN: Quality of life – Diabetic Neuropathy; RCT: randomized controlled trial; TTR-FAP: transthyretin familial amyloid polyneuropathy; Val30Met: replacement of valine by methionine at Position 30 of the aminoacid sequence.

Table 4: Characteristics of the interventions in the studies with tafamidis

Study	Tafamidis	Placebo
Randomized controlled trial		
Fx-005	20 mg tafamidis once daily orally	Placebo once daily orally
	Concomitant medication (in both arms): Concomitant medication could be used at the discretion of the investigators. Drugs with a narrow therapeutic index (such as warfarin and digoxin) were to be used with caution. The following treatments were not permitted: ▪ Chronic use of NSAIDs (defined as ingestion > 3 to 4 times per month); but the following NSAIDs were allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, sulindac. ▪ Liver transplantation (patients who received a liver transplant discontinued the study)	
Other investigation: non-controlled study		
Fx1A-201	20 mg tafamidis once daily orally for 12 months	–
	Concomitant medication: Concomitant medication could be used. The following treatments were not permitted: ▪ Chronic use of NSAIDs (defined as ingestion > 3 to 4 times per month); but the following NSAIDs were allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, sulindac. ▪ Liver transplantation (patients who received a liver transplant discontinued the study)	

NSAIDs: Non-steroidal anti-inflammatory drugs.

The co-primary outcomes of the RCT Fx-005 were response (measured using a pre-defined response criterion on the NIS-LL scale for measurement of neurological impairment) and health-related quality of life (measured using the Norfolk QOL-DN). The primary outcome of the Fx1A-201 study was the stabilization of the TTR tetramer in Week 6, compared with the baseline value.

The study duration was 18 months in the RCT Fx-005 and 12 months in the non-controlled Fx1A-201 study.

The permitted concomitant medications were similar in both studies.

Table 5 shows the characteristics of patients in the studies included.

Table 5: Characteristics of the study populations in the studies with tafamidis

Study Group	Mutation	N	Study discont. n (%)	Age in years mean (SD) median [range]	Sex f/m (%)	Duration of TTR-FAP symptoms in months mean (SD) median [range]	Baseline NIS-LL mean (SD) median [range]
Randomized controlled trial							
Fx-005							
Tafamidis/BSC	Val30Met	64[a]	18 (28)	40 (13) 36 [25;74]	50/50	47 (48) 28 [3;268]	8.4 (11.4) 4.0 [0;54]
Placebo/BSC		61[a]	19 (30)	38 (13) 34 [22;71]	57/43	35 (33) 21 [2;133]	11.4 (13.5) 6.0 [0;57]
Other investigation: non-controlled study							
Fx1A-201							
Tafamidis/BSC	non-Val30Met	21[b]	3 (14)	63 (10) 64 [44;77]	38/62	65 (61) 46 [5;253]	27.6 (24.7) 18.0 [0;70]

a: Number of patients in the ITT analysis.
b: Number of enrolled patients.

BSC: best supportive care; discont.: discontinuations; ITT: intention-to-treat; f: female; m: male; N: number of patients in the analysis; n: number of patients with event; NIS-LL: Neuropathy Impairment Score in the Lower Limbs; SD: standard deviation; TTR-FAP: transthyretin familial amyloid polyneuropathy; Val30Met: replacement of valine by methionine at Position 30 of the aminoacid sequence.

The RCT Fx-005 enrolled exclusively patients with Val30Met mutation, whereas the non-controlled Fx1A-201 study investigated patients with non-Val30Met mutations.

Although the number of study discontinuations in the RCT is comparable in the 2 arms, it is nonetheless high overall. The company states that the study was mostly discontinued because of liver transplantations (13 patients in each arm received a liver transplant). Patients who received a liver transplant also made up the majority of study discontinuations in the non-controlled study (2 out of 3 patients). The impact of the patients who discontinued the study due to a liver transplant on the results is discussed in the context of the imputation methods in Section 2.7.2.4.2 of the full dossier assessment.

The average age of patients in the RCT Fx-005 was about 40 years. Considerably older patients were enrolled in the non-controlled study. In the RCT Fx-005, the mean duration of TTR-FAP symptoms was longer in the tafamidis arm than in the placebo arm. On the other hand, the neurological impairment, measured with the NIS-LL, was greater in the placebo arm. The duration of symptoms was longer and the neurological impairment was more advanced in the non-controlled Fx1A-201 study than in the RCT. Overall, the patient populations in the two studies differed substantially.

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level for studies with tafamidis

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Selective outcome reporting	Other sources of bias	Risk of bias at study level
			Patients	Treating persons			
Randomized controlled trial							
Fx-005	yes	yes	yes	yes	no	no	low
Other investigations: non-controlled study							
Fx1A-201				high[a]			
a: Non-controlled study, see Section 2.7.2.7 of the full dossier assessment.							

The risk of bias at study level was rated as low for the RCT. This concurs with the company's assessment in the dossier.

The risk of bias for the non-controlled study could not be assessed using the same method as for comparative studies. With non-comparative studies, a high risk of bias is generally assumed at study and outcome levels (see Section 2.7.2.7 of the full dossier assessment). The company gives no reasons for a deviation from this general assessment of the risk of bias of non-controlled studies for the Fx1A-201 study. The company itself rates the informative value of its non-controlled study as "low" (see Section 4.3.2.3.2.2 in the dossier).

Further information about the study design, study populations and risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1. 4.3.1.2.2 and 4.3.2.1.2 of the dossier and in Sections 2.7.2.4.1. 2.7.2.4.2 and 2.7.2.7 of the full dossier assessment.

2.4 Results concerning added benefit

The following patient-relevant outcomes were included in the assessment (for justification, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - Neurological impairment (NIS-LL response)
- Health-related quality of life
  - Norfolk Quality of Life – Diabetic Neuropathy Score (QOL-DN), Short-Form 36 (SF-36)
- Adverse events
  - Adverse events

- Serious adverse events
- Discontinuation due to adverse events
- Adverse events, gastrointestinal events
- Adverse events, infections

The Institute choice of patient-relevant outcomes deviates from that of the company, which used other outcomes in the dossier (Module 4) for morbidity and gave no information about specific adverse events (see Section 2.7.2.4.3 of the full dossier assessment for justification of the choice of outcomes by the Institute).

Table 7 shows for which outcomes data were available in the studies included. Table 8 describes the risk of bias for these outcomes.

Table 7: Matrix of outcomes for studies with tafamidis

Study	**All-cause mortality**	**Neurological impairment (NIS-LL response)[a]**	**Health-related quality of life (QOL-DN)**	**Health-related quality of life (SF-36)**	**Adverse events**	**Serious adverse events**	**Discontinuation due to adverse events**	**Gastrointestinal events**	**Infections**
Randomized controlled trial									
Fx-005	yes	yes	yes	no	yes	yes	yes	yes	yes
Other investigations: non-controlled study									
Fx1A-201	yes	no[b]	yes	yes	yes	yes	yes	yes	yes

a: Measured value interpreted as proportion of patients without progression of neurodegeneration, see Section 2.7.2.4.3 of the full dossier assessment.

b: In the non-controlled study, only the continuous assessment of the NIS-LL data was carried out.

NIS-LL: Neuropathy Impairment Score in the Lower Limbs; QOL-DN: Norfolk Quality of Life – Diabetic Neuropathy; SF-36: Short-Form 36.

Table 8: Risk of bias at study and outcome level for studies with tafamidis

Study	Study level	Outcome							
		All-cause mortality	**Neurological impairment (NIS-LL response)[b]**	**Health-related quality of life**	**Adverse events**	**Serious adverse events**	**Discontinuation due to adverse events**	**Gastrointestinal events**	**Infections**
Randomized controlled trial									
Fx-005	low	high[a]	high[c]	low	low	low	low	low	low
Other investigations: non-controlled study									
Fx1A-201		high[d]							

a: All reported deaths occurred after liver transplantation, but it is not clear whether all patients who received a liver transplant were systematically followed-up.

b: Proportion of patients with response, interpreted as proportion of patients without progression of neurodegeneration, see Section 2.7.2.4.3 of the full dossier assessment.

c: Different imputation methods for missing values at the end of the study for the 26 patients (20%) who had to discontinue the study prematurely because of a liver transplantation lead to different conclusions regarding the statistical significance.

d: Non-controlled study, see Section 2.7.2.7 of the full dossier assessment.

NIS-LL: Neuropathy Impairment Score in the Lower Limbs.

The Institute rated the risk of bias for most of the outcomes recorded in the RCT as low. However, for all-cause mortality and neurological impairment (NIS-LL response) the risk of bias was rated as high (for justification, see Table 8).

The company assessed the risk of bias in the RCT at outcome level generally as low. The company did not assess the risk of bias for the outcome "mortality", because this outcome was not included in its assessment. The Institute's assessment thus deviates from that of the company with regard to the outcome measured using the NIS-LL. For a discussion of the results on neurological impairment, measured using the NIS-LL, and on the response criterion, see Section 2.7.2.4.3 of the full dossier assessment.

For the non-controlled study, the company assessed aspects of bias at outcome level (blinding of outcome assessors, adequate implementation of the intention-to-treat (ITT) principle, potential selective outcome reporting and other points influencing the risk of bias). For example, the influence of a validation of the instruments tailored to the therapeutic indication is discussed. Although the content of the discussion about outcomes is helpful, overall this method cannot be accepted. The risk of bias at study and outcome level for non-controlled studies is to be assessed per se as "high" (see Section 2.7.2.7 of the full dossier assessment).

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2, 2.7.2.4.3 and 2.7.2.7 of the full dossier assessment.

Table 9 and Table 10 summarize the results on the comparison of tafamidis/BSC and placebo/BSC in adult patients diagnosed with TTR-FAP. It should be noted that exclusively patients with a mutation of the Val30Met type were enrolled in the RCT Fx-005, whereas TTR-FAP patients with other, i.e. non-Val30Met mutations, were investigated in the non-controlled Fx1A-201 study.

Where necessary, data from the dossier were supplemented by the Institute's own calculations. Because of the different design of the 2 studies included in the assessment, no meta-analyses could be undertaken.

As already explained in Section 2.3.2, the line of reasoning of the company on the transferability of the effect direction of positive effects between patients with Val30Met mutation and non-Val30Met mutation was taken into account for the assessment of tafamidis as a drug for the treatment of an orphan disease. The results shown in Table 9 for the RCT Fx-005 in patients with Val30Met mutation are therefore the basis for the assessment of tafamidis; the uncertainty in relation to the assessment of tafamidis in the treatment of patients with non-Val30Met mutation associated with the described approach must be taken into account. A discussion of the interpretation of the non-controlled study can be found in Section 2.7.2.7 of the full dossier assessment.

The results are presented grouped according to mortality, health-related quality of life and adverse events. Dichotomous and continuous data are shown in separate tables.

Table 9: Results on mortality, morbidity and adverse events (dichotomous outcomes) from studies with tafamidis

Outcome Study	Tafamidis/BSC		Placebo/BSC		Tafamidis/BSC vs. placebo/BSC	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	p-value
Mortality						
All-cause mortality						
Fx-005	65	1 (1.5)[b]	63	3[c] (4.8)[b]	0.32 [0.04; 3.02][b]	0.320[b]
Fx1A-201	21	0 (0)				
Morbidity						
Neurological impairment (response)[d]						
NIS-LL response (ITT-LOCF)[e]						
Fx-005	64	29 (45.3)	61	18 (29.5)	1.54 [0.96; 2.46][b]	0.073[b]
Fx1A-201	21		Outcome not investigated			
NIS-LL response, sensitivity analysis (ITT-LOCF)[f]						
Fx-005	64	35 (54.7)	61	22 (36.1)	1.52 [1.02; 2.27][b]	0.037[b]
Fx1A-201	21		Outcome not investigated			
Adverse events						
Adverse events (AEs)						
Fx-005	65	60 (92.3)	63	61 (96.8)	0.95 [0.88; 1.04][b]	0.270[b]
Fx1A-201	21	17 (81.0)		–	–	–
Serious adverse events (SAEs)						
Fx-005	65	6 (9.2)	63	5 (7.9)	1.16 [0.37; 3.62][b]	0.845[b]
Fx1A-201	21	8 (38.1)		–	–	–
Treatment discontinuations due to adverse events						
Fx-005	65	4 (6.2)	63	3 (4.8)	1.29 [0.30; 5.54][b]	0.805[b]
Fx1A-201	21	1 (4.8)		–	–	–
Adverse events: gastrointestinal events[g]						
Fx-005	65	35 (53.8)	63	39 (61.9)	0.87 [0.65; 1.17][b]	0.517[b]
Fx1A-201	21	7 (33.3)		–	–	–
Adverse events: infections[g]						
Fx-005	65	43 (66.2)	63	33 (52.4)	1.26 [0.94; 1.69][b]	0.123[b]
Fx1A-201	21	8 (38.1)		–	–	–

(continued on next page)

Table 9: Results on mortality, morbidity and adverse events (dichotomous outcomes) from studies with tafamidis (continuation)

a: Number of analysed patients.
b: Institute's calculation: percentages, relative risk and p-value from unconditional exact test, CSZ method according to [4].
c: One death was only reported after database closure.
d: Response criterion: change < 2 points on the NIS-LL scale; i.e. no progression of neurological impairment (see Section 2.7.2.4.3 of the full dossier assessment).
e: Patients who discontinued the study prematurely because of liver transplantation (N = 26) were analysed as non-responders, the missing values of discontinuations for other reasons (N=11) were imputed according to the LOCF method.
f: Missing values at the end of the study for patients who discontinued the study prematurely due to liver transplantation (N = 26) were replaced by a logistical regression model (the probability of a response for these patients who discontinued in the respective treatment groups was estimated for both treatments with the median baseline NIS-LL of patients who received a transplant), the missing values of patients who discontinued prematurely for other reasons (N = 11) were replaced with the LOCF method.
g: Events coded with the MedDRA System Organ Class definitions ("Gastrointestinal disorders" and "Infections and infestations").

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, Z-score; ITT: Intention-to-treat; LOCF: Last Observation Carried Forward; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in analysis; n: number of patients with event; NIS-LL: Neuropathy Impairment Score in the Lower Limbs; RR: relative risk; SAE: serious adverse event.

Table 10: Results on health-related quality of life (continuous outcomes) from studies with tafamidis

Study Scale Intervention	N[a]	Value at start of study mean (SD)	Change at end of study mean (SE)	Difference in means [95% CI]	p-value
Health-related quality of life: Norfolk QOL-DN					
Fx-005					
Tafamidis/BSC	64	27.3 (24.17)	2.7 (2.83)[b]	-5.1 [-13.1; 2.9][b]	0.209 [b]
Placebo/BSC	61	30.8 (26.72)	7.8 (2.86)[b]		
Fx1A-201					
Tafamidis/BSC	21	47.8 (35.14)	0.1 (18.01)[c]		
Health-related quality of life: SF-36					
Fx-005			Outcome not investigated		
Fx1A-201					
Sum score “physical health”					
Tafamidis/BSC	21	36.2 (11.90)	-0.4 (8.47)[c]		
Sum score “mental health”					
Tafamidis/BSC	21	47.0 (10.96)	3.0 (11.11) [c]		

a: Number of analysed patients.
b: LS mean, SE and CI and p-value from an analysis of variance with repeated measures based on linear mixed models (repeated measures analysis of variance).
c: Values for observed cases at end of study (n = 18), standard deviation in brackets.
BSC: best supportive care; CI: confidence interval; LS: least square; N: number of patients in the analysis; QOL-DN: Norfolk Quality of Life – Diabetic Neuropathy; SE: standard error; SD: standard deviation; SF-36: Short Form 36.

Mortality

The RCT Fx-005 in patients with Val30Met mutation showed no statistically significant difference for the outcome “overall survival” between the treatment groups. Only a few deaths were recorded, all of which occurred after a liver transplantation. No deaths occurred in the non-controlled study Fx1A-201 in patients with a non-Val30Met mutation.

Overall, no added benefit of tafamidis in combination with BSC compared to BSC alone can be derived for the outcome “overall survival”.

The company presented no data on mortality in Module 4 of the dossier and hence drew no conclusions about the added benefit of tafamidis with regard to this outcome.

Morbidity

Neurological impairment (NIS-LL response)

A responder analysis was used for the benefit assessment for the outcome “neurological impairment”, measured with the NIS-LL (for detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment). In this analysis, response is defined as an increase of less than 2

points of the NIS-LL total score. This definition means that either no change in the neurological findings (change of 0 points) took place, or that with this generally symmetrically progressing disease a change of 1 point was only diagnosed on one side. Taking into account the limited severity of the neurological impairment in the patient population with TTR-FAP in the early stage of the disease, in the Institute's view this response appears suitable for determining the proportion of patients without progression of neurodegeneration in the submitted study. In the present constellation (symptoms not very marked, a delay in the reduction in the peripheral neurological functional capacity as the treatment aim), this responder analysis of the NIS-LL is rated as a patient-relevant outcome.

Results of the responder analysis were available only from the RCT Fx-005. Two analyses were used for the benefit assessment in which - in addition to the LOCF analysis for patients who discontinued the study prematurely for reasons other than a liver transplantation – different imputation methods were used for patients who discontinued the study because of a liver transplantation (for detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment). The proportion of patients who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher under tafamidis/BSC than under placebo/BSC in both analyses. One of the analyses (replacement of missing values by non-response values for patients who discontinued due to liver transplantation) showed no statistically significant difference between the treatment groups at a significance level of α=0.05; the second analysis (replacement of missing values by values from logistic regression for patients who discontinued due to liver transplantation) produced a statistically significantly higher proportion of patients without progression of the neurodegeneration in the group who received tafamidis. In addition, there is an analysis of responder data requested by the European Medicines Agency (EMA) for the approval of the drug, in which the uncertainty caused by the replacement was taken into account by a multiple imputation method. This showed no statistically significant difference (p = 0.125) between the two treatment groups [3]. Taken as a whole, these results are rated as a hint of a positive effect of tafamidis in combination with BSC compared to BSC alone. The symptoms of the neurological impairment in the study population included are not particularly pronounced and the impairment cannot be classed as severe symptoms. Due to the marginal effect size for non-severe symptoms, no added benefit is derived from the effect for the outcome "neurological impairment".

In the RCT Fx-005, only patients with Val30Met mutation were enrolled, so that, in the first instance, the hint of an effect in relation to neurological impairment applies only to these patients. On the basis of the data presented by the company in the dossier, the Institute assumes that positive effects of tafamidis in the patient populations with Val30Met mutation go in the same direction in the population with non-Val30Met mutation. However, it remains unclear whether a comparable effect size can be assumed for positive effects (in the case of negative effects, both the direction and size of effect remain unclear, see Section 2.7.2.7 of the full dossier assessment).

Although no responder analysis of the NIS-LL was undertaken for the Fx1A-201 study, on the basis of the available continuous data, the assumption of the same direction of effect for neurological impairment in patients with non-Val30Met mutation appears justified. Overall, from the results of the RCT Fx-005, a hint is derived of a positive effect of tafamidis in combination with BSC in patients with non-Val30Met mutation for the outcome "neurological impairment". Whether the effect is large enough to show an added benefit for patients with non-Val30Met mutation with regard to this outcome remains unclear.

Health-related quality of life

Health-related quality of life of the patients was recorded in both studies with an instrument (Norfolk QOL-DN 35-item questionnaire) validated for diabetic neuropathy and rated as suitable for the TTR-FAP population. The RCT in patients with Val30Met mutation on average showed that patients' health-related quality of life deteriorated during the course of the study in both treatment groups. Comparison of the change in health-related quality of life showed no statistically significant difference between the treatment groups.

In the non-controlled study in patients with non-Val30Met mutation, health-related quality of life, measured with the Norfolk QOL-DN, on average remained unchanged. The assessment of health-related quality of life with the SF-36 also showed, on average, no marked changes.

Hence, in patients with TTR-FAP, no added benefit of tafamidis in combination with BSC compared to BSC alone can be derived for health-related quality of life.

Adverse events

The RCT Fx-005 in patients with Val30Met mutation showed no statistically significant difference between tafamidis/BSC and placebo/BSC for the overall rate of adverse events, the overall rate of serious adverse events, the overall rate of treatment discontinuations due to adverse events or the overall rate of gastrointestinal events and infections.

The overall rate of serious adverse events under tafamidis/BSC was higher in the non-controlled Fx1A-201 study in patients with non-Val30Met mutation than in the RCT. The proportion of patients with adverse events of the gastrointestinal tract or with infections was, on the other hand, lower than in the RCT. Since the Fx1A-201 study had no control group, it remains unclear whether the observed adverse events were related to the treatment with tafamidis. The study allowed no conclusions about the harm from tafamidis/BSC in patients with non-Val30Met mutation.

Hence, a lesser/greater harm from tafamidis in combination with BSC compared to BSC alone cannot be derived for the outcomes named above.

Further information about the choice of outcome, the risk of bias at outcome level and the outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2, 2.7.2.4.3 as well as 2.7.2.7 and 2.7.2.9.4 of the full dossier assessment.

Assessment of added benefit by the company

In a preamble to Section 4.4.4 of the dossier, the company maintains that, in its view, the G-BA has to ascribe the highest degree of added benefit to an orphan drug below a turnover threshold of 50 million Euro because, in accordance with § 35a SGB V, the legislator accords a privileged position to orphan drugs in the benefit assessment and the resulting pricing negotiations. In the company's view, a major added benefit of tafamidis is proven. In addition, in an outcome-related quantification of the added benefit in Section 4.4.4 of the dossier, the company describes the added benefit for the outcomes NIS-LL original scale, NIS-LL responder analysis, health-related quality of life and modified body mass index (BMI) as major. The company draws no conclusions about the added benefit on the basis of the data on adverse events.

2.5 Extent and probability of the added benefit

The effects of tafamidis in combination with BSC for the 2 subpopulations (according to mutation status) at outcome level are summarized below (see Table 11).

Table 11: Tafamidis + BSC vs. BSC in patients with TTR-FAP – summary of the effects at outcome level

Outcome Mutation type[a]		**Effect estimator [95% CI]** **Proportion of events tafamidis/BSC vs. placebo/BSC** **p-value** **Probability**
Mortality		
All-cause mortality	TTR mutation type Val30Met	RR 0.32 [0.04; 3.02] 1.5 % vs. 4.8 % p = 0.320
	TTR mutation type non-Val30Met	Probably same effect direction as in the subpopulation with Val30Met mutation; but effect size unclear
Morbidity		
Neurological impairment (proportion of patients without progression of neuro-degeneration)	TTR mutation type Val30Met	Results from the analyses with different replacement strategies for patients with liver transplantation, that are of equal value in the overall picture[b]: RR 1.54 [0.96; 2.46] RR 1.52 [1.02; 2.27] RR 0.65 [0.41; 1.04] [c] RR 0.66 [0.44; 0.99][c] 45.3 vs. 29.5 % 54.7 % vs. 36.1 % p = 0.073 p = 0.037 Probability: "hint"
	TTR mutation type non-Val30Met	Probably same effect direction as in the subpopulation with Val30Met mutation; but effect size unclear Probability: "hint"
Norfolk QOL-DN	TTR mutation type Val30Met	Mean difference: -5.1 [-13.1; 2.9] points p = 0.209
	TTR mutation type non-Val30Met	Probably same effect direction as in the subpopulation with Val30Met mutation; but effect size unclear
SF-36	TTR mutation type Val30Met	No data recorded
	TTR mutation type non-Val30Met	Effect size unclear
Adverse events		
Adverse events	TTR mutation type Val30Met	RR 0.95 [0.88; 1.04] 92.2 % vs. 96.8 % p = 0.270
	TTR mutation type non-Val30Met	Direction and size of effect unclear
Serious adverse events	TTR mutation type Val30Met	RR 1.16 [0.37; 3.62] 9.2 % vs. 7.9 % p = 0.845
	TTR mutation type non-Val30Met	Direction and size of effect unclear

(continued on next page)

Table 11: Tafamidis + BSC vs. BSC in patients with TTR-FAP – summary of the effects at outcome level (continued)

Outcome Mutation type[a]		**Effect estimator [95 % CI]** **Proportion of events tafamidis/BSC vs. placebo/BSC** **p-value**
Adverse events		
Discontinuation due to adverse events	TTR mutation type Val30Met	RR 1.29 [0.30; 5.54] 6.2 % vs. 4.8 % p = 0.805
	TTR mutation type non-Val30Met	Direction and size of effect unclear
Adverse events of the gastrointestinal tract	TTR mutation type Val30Met	RR 0.87 [0.65; 1.17] 53.8 % vs. 61.9 % p = 0.517
	TTR mutation type non-Val30Met	Direction and size of effect unclear
Adverse events: infections	TTR mutation type Val30Met	RR 1.26 [0.94; 1.69] 66.2 % vs. 52.4 % p = 0.123
	TTR mutation type non-Val30Met	Direction and size of effect unclear

a: Separate presentation of the subpopulations according to mutation type because of different population characteristics and different evidence base for the benefit assessment (for justification, see Section 2.7.2.7 of the full dossier assessment).

b: In one analysis, patients who discontinued prematurely due to liver transplantation were replaced by non-response, in a sensitivity analysis using a logistical regression model. No clear hierarchical analysis of the adequacy of the replacement strategies was possible.

c: Institute's calculations, proportion of events placebo/tafamidis (direction of effect reversed to assess the effect size).

BSC: best supportive care; CI: confidence interval; RR: relative risk; SF-36: Short Form 36; Val30Met: mutation at Position 30 of the aminoacid sequence of the transthyretin gene leads to a replacement of the aminoacid valine by methionine.

The overall conclusion on the added benefit results from the statutory basis for the assessment of orphan drugs.

In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved. The decision on the extent of added benefit is made by the G-BA.

Additional comments of IQWiG

An assessment of the available data according to the methods of IQWiG on the basis of responder analysis of the NIS-LL from the RCT Fx-005 would first have led to a hint of a positive effect of tafamidis in combination with BSC compared to BSC alone in terms of the progression of neurological degeneration in patients with TTR-FAP. The effect size would

not, however, have been sufficient to derive an added benefit in terms of this outcome for the non-severe symptoms present in the RCT study population.

Even if the Institute accepted a higher degree of uncertainty (in accordance with the proposal from the National Institute for Clinical Excellence (NICE) regarding an "Ultra Orphan" definition, significance level $\alpha = 0.10$), no effect sizes would have arisen in the 2 analyses of NIS-LL that could have been interpreted as added benefit, given the non-severe symptoms (RR [90% CI] placebo/BSC vs. tafamidis/BSC: 0.65 [0.44; 0.97] for the primary analysis; 0.66 [0.47; 0.92] for the sensitivity analysis).

Other statistically significant effects of tafamidis regarding patient-relevant outcomes were not identified in the present assessment.

2.6 List of included studies

Study Fx-005

European Medicines Agency. Vyndagel: EMEA/H/C/002294; rapporteurs' day 180 joint response assessment report [unpublished]. 2011.

FoldRx Pharmaceuticals. Safety and efficacy of orally administered tafamidis (Fx-1006A) in patients with Familial Amyloid Polyneuropathy (FAP): a phase II/III, randomized, double-blind, placebo-controlled study: study Fx-005; clinical study report [unpublished]. 2010.

FoldRx Pharmaceuticals. Safety and efficacy of orally administered tafamidis (Fx-1006A) in patients with Familial Amyloid Polyneuropathy (FAP): a phase II/III, randomized, double-blind, placebo-controlled study: study Fx-005; clinical study protocol [unpublished]. 2006.

FoldRx Pharmaceuticals. Safety and efficacy of orally administered tafamidis (Fx-1006A) in patients with Familial Amyloid Polyneuropathy (FAP): a phase II/III, randomized, double-blind, placebo-controlled study: study Fx-005; statistical analysis plan [unpublished]. 2008.

Packman J. Safety and efficacy study of Fx-1006A in patients with familial amyloidosis [online]. In: ClinicalTrials.gov. 25.05.2011 [Accessed on: 07.11.2011]. URL: http://clinicaltrials.gov/ct2/show/NCT00409175.

Packman J. Safety and efficacy study of Fx-1006A in patients with familial amyloidosis [online]. In: International Clinical Trials Registry Platform. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00409175.

Study Fx1A-201

European Medicines Agency. Vyndagel: EMEA/H/C/002294; rapporteurs' day 180 joint response assessment report [unpublished]. 2011.

FoldRx Pharmaceuticals. The effects of Fx-1006A on transthyretin stabilization and clinical outcome measures in patients with non-V30M transthyretin amyloidosis: study Fx1A-201; clinical study report [unpublished]. 2010.

FoldRx Pharmaceuticals. The effects of Fx-1006A on transthyretin stabilization and clinical outcome measures in patients with non-V30M transthyretin amyloidosis: study Fx1A-201; statistical analysis plan [unpublished]. 2009.

FoldRx Pharmaceuticals. The effects of Fx-1006A on transthyretin stabilization and clinical outcome measures in patients with non-V30M transthyretin amyloidosis: study Fx1A-201; clinical protocol amendment 2 [unpublished]. 2008.

Pfizer. The effects of Fx-1006A on transthyretin stabilization and clinical outcome measures in patients with non-V30M transthyretin amyloidosis [online]. In: ClinicalTrials.gov. 03.06.2011 [Accessed on: 07.11.2011]. URL: http://clinicaltrials.gov/ct2/show/NCT00630864.

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Please see full dossier assessment for full reference list**.**

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