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CADTH COMMON DRUG REVIEW

Clinical Review Report

TAFAMIDIS (Vyndaqel)

(Pfizer Canada ULC)

Indication: For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.

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Abbreviations

6MWT	six-minute walk test
AE	adverse event
ANCOVA	analysis of covariance
ATTR	transthyretin-mediated amyloidosis
ATTR-CM	transthyretin-mediated amyloidosis cardiomyopathy
BMI	body mass index
CASN	Canadian Amyloidosis Support Network
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CMAD	cardiac mechanical assist device
CORD	Canadian Organization for Rare Disorders
EGCG	epigallocatechin-3-gallate
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
EQ VAS	EuroQol Visual Analogue Scale
GLS	global longitudinal strain
hATTR	hereditary transthyretin-mediated amyloidosis
hATTR-CM	hereditary transthyretin-mediated amyloidosis cardiomyopathy
hATTR-PN	hereditary transthyretin-mediated amyloidosis with polyneuropathy
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
LVEF	left ventricular ejection fraction
mBMI	modified body mass index
MCID	minimum clinically important difference
MMRM	mixed model with repeated measures
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PGA	Patient Global Assessment
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
TTR	transthyretin
wATTR-CM	wild-type transthyretin-mediated amyloidosis cardiomyopathy

Drug	Tafamidis meglumine (Vyndaqel)
Indication	For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.
Reimbursement request	Treatment of transthyretin amyloid cardiomyopathy in adult patients.
Dosage form(s) and route of administration) and strength(s)	20 mg capsule
NOC date	January 20, 2020
Sponsor	Pfizer Canada ULC

Executive Summary

Introduction

Transthyretin (TTR) amyloidosis is a life-threatening progressive disease that occurs in hereditary and wild-type forms. The hereditary form is caused by genetic mutations that destabilize the TTR protein. The mutation that is most commonly associated with cardiomyopathy is V122I. The wild-type form is not due to a genetic mutation and amyloid can also deposit into tissues to cause an age-related amyloidosis that primarily affects men aged 60 years and older (later than hereditary forms). TTR-mediated amyloidosis (ATTR) cardiomyopathy (ATTR-CM) occurs when TTR amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure and, ultimately, death.[1,2,3] The clinical presentation of ATTR-CM varies widely, from asymptomatic to severely progressive heart failure. Symptoms of ATTR-CM are typical of restrictive cardiac disease and include dyspnea on exertion, orthostatic hypotension, and syncope, as well as conduction abnormalities, including bundle branch block, atrioventricular block, sinoatrial block, and atrial fibrillation.[4,5] Common causes of death in this disease are progressive heart failure and sudden cardiac death. Aside from supportive cardiac disease management, treatment options to address the underlying disease process are limited.

Tafamidis meglumine is a small molecule that stabilizes the TTR protein in both wild-type and hereditary forms of ATTR-CM. It is available as a 20 mg capsule that is taken orally. The Health Canada indication for tafamidis meglumine 80 mg (administered as four 20 mg capsules) is for the treatment of adult patients with cardiomyopathy due to ATTR, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.[6]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of tafamidis meglumine 80 mg for the treatment of adult patients with cardiomyopathy due to wild-type or hereditary ATTR (hATTR).

Stakeholder Engagement

Patient Input

The Canadian Organization for Rare Disorders (CORD) with the support of the Canadian Amyloidosis Support Network (CASN) provided input for this review. An online survey was completed by 42 patients/caregivers and individual interviews were held with four patients. Nearly all respondents reported that the condition was debilitating, interfering significantly with daily functioning and quality of life. Prior to tafamidis, there were no therapies available specifically for ATTR-CM. Responders' experience on tafamidis treatment are optimistic. Tafamidis had an impact on symptoms, namely, a reduction in nerve pain, an increase in strength and energy, better appetite, improved mobility, and improvement in quality of life. Responders unanimously called for the availability of tafamidis to patients with ATTR-CM (hereditary or wild-type), regardless of disease status.

Clinician Input

The following input is a summary of information provided by three clinical specialists with expertise in the diagnosis and management of ATTR.

There is an unmet need for disease-modifying treatments that address the underlying pathology of ATTR-CM. There is no treatment currently available that is supported by robust evidence for hereditary ATTR with pure cardiomyopathy phenotype or for any wild-type ATTR disease. The currently available treatments (e.g., diflunisal) lack evidence, are limited by side effects, and none are known to reverse, or stabilize, disease. Tafamidis is expected to shift the current treatment paradigm for ATTR-CM and would be considered as a first-line treatment for eligible patients.

It is anticipated that patients who will benefit the most from treatment will be those with less advanced disease. Patients in New York Heart Association (NYHA) class I to III are likely to derive benefit from treatment. It is unclear if patients with hereditary TTR-mediated amyloidosis cardiomyopathy (hATTR-CM) who are pre-symptomatic (i.e., gene mutation identified but no presentation of symptoms) would be suitable for treatment with tafamidis. However, patients who are asymptomatic, but with an established diagnosis of ATTR and clear cardiac involvement, should be treated. Patients with end-stage or advanced disease (i.e., NYHA class IV) are least likely to benefit from treatment with tafamidis.

A subjective assessment of patients' symptoms and NYHA functional class (severity of heart failure symptoms and exercise tolerance) would be used to determine if a patient is responding to treatment in clinical practice. A clinically meaningful response to treatment would be the absence of any disease progression or disease stabilization. In the early stages of disease, response to treatment should be assessed every six months, but as patients develop heart failure they will need to be assessed more frequently; the frequency of assessment will vary with disease severity.

Aside from adverse events (AEs), there is no anticipated clear indication to stop treatment with tafamidis. It is expected that tafamidis will be a lifelong treatment, even in patients who have been on the drug for some time and have experienced disease progression.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The ATTR-ACT study was a phase III, double-blind, randomized controlled trial (RCT) in adults with hereditary or wild-type ATTR-CM. A total of 441 patients were randomized in a 2:1:2 ratio to placebo (N = 177), tafamidis 20 mg (N = 88), or tafamidis 80 mg (N = 176) once daily for 30 months. Randomization was stratified by wild-type or hereditary ATTR-CM, and NYHA class. The primary outcomes were a hierarchical combination of all-cause mortality and cardiovascular-related hospitalization at month 30, assessed using the Finkelstein-Schoenfeld method. Key secondary outcomes were the six-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, which were tested as part of a statistical hierarchy to control for multiplicity. Another secondary outcome was cardiovascular-related mortality, and exploratory outcomes were all-cause hospitalization, generic health-related quality of life (HRQoL), Patient Global Assessment (PGA), change in NYHA classification, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), echocardiogram parameters, and modified body mass index (mBMI); none of these outcomes were controlled for multiplicity. Exploratory subgroup analyses were conducted for the pooled tafamidis group versus placebo by TTR genotype (wild-type or hereditary) and NYHA baseline classification (class I/II combined or class III).

The Health Canada–recommended dose of tafamidis is 80 mg and is the focus of this review.

Efficacy Results

Key efficacy results are summarized in Table 1.

At month 30, more patients were alive in the tafamidis 80 mg group compared with placebo (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with tafamidis 80 mg among patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). In the primary analysis that compared the pooled tafamidis dose group with placebo, the results demonstrated a pattern that was similar to tafamidis 80 mg. The Finkelstein-Schoenfeld analysis was statistically significant for the pooled tafamidis group versus placebo (P = 0.0006), demonstrating that at least one or possibly both outcomes (all-cause mortality and cardiovascular-related hospitalization) were statistically significantly different. Results of the per-protocol analysis were consistent with the primary analysis. For patients with wild-type TTR-mediated amyloidosis cardiomyopathy (wATTR-CM), more patients in the tafamidis pooled group were alive at month 30 and, among those who were alive, there were fewer cardiovascular-related hospitalizations compared with placebo. For patients with hATTR-CM, more patients in the tafamidis pooled group were alive at month 30 compared with placebo. It was also observed that the cardiovascular-related hospitalization among patients who were alive was higher for the tafamidis pooled group versus placebo based on an exploratory subgroup analysis. In patients with an NYHA classification of I or II at baseline, more patients who received tafamidis were alive at month 30 and cardiovascular-related hospitalization was lower compared with placebo. In patients with an NYHA classification of III at baseline, slightly more patients were alive at month 30; however, cardiovascular-related hospitalizations were higher compared with placebo.

Exploratory analyses were conducted to investigate all-cause and cardiovascular-related causes of death and hospitalizations. All causes of death (patients with a transplant or cardiac mechanical assist device [CMAD] were not treated as death) occurred in 40.7% of patients in the placebo group, 27.8% of patients in the tafamidis 80 mg group, and 27.3% in the pooled tafamidis group. Cardiovascular causes of death occurred in 28% of patients in the placebo group, 20.5% of patients in the tafamidis 80 mg group, and 20% of patients in the pooled tafamidis group. The rate ratio for all-cause hospitalizations for the pooled tafamidis group versus placebo was 0.79 (95% confidence interval [CI], 0.69 to 0.91). The rate ratio for cardiovascular-related hospitalizations was 0.68 (95% CI, 0.56 to 0.81).

For the key secondary outcome of KCCQ overall score, the least squares mean difference in change from baseline for the pooled tafamidis group versus placebo was 13.7 points (95% CI, 9.5 to 17.8). In exploratory analysis, the least squares mean difference for tafamidis 80 mg versus placebo was 13.5 points (9.2 to 17.8). These estimates exceed the minimal clinically important difference (MCID) of 5.7 for patients with congestive heart failure. In the exploratory subgroup analysis, the change from baseline to month 30 on the KCCQ was smaller in the negative direction (indicating less worsening of health) in the pooled tafamidis group compared with the placebo group for all subgroups.

Disability was measured using the 6MWT. The decrease in the 6MWT from baseline to month 30 was smaller for tafamidis 80 mg compared with placebo (least squares mean change = −54.8 metres versus −130.6 metres). Similarly, for the pooled tafamidis group, the decrease was smaller compared with placebo (−54.9 metres). The least squares mean difference for the pooled tafamidis group versus placebo was 75.7 metres (95% CI, 57.6 to 93.8). Although no MCID for the 6MWT test is available specifically for patients with ATTR-CM, these estimates exceeded the MCID of 43 metres for heart failure. In all subgroups, the decrease in the distance walked from baseline to month 30 was smaller for the pooled tafamidis group compared with placebo. However, for patients with NYHA class III at baseline, the magnitude of the difference between placebo and tafamidis was smaller than for the other subgroups.

The NT-proBNP level in both the pooled tafamidis and placebo groups increased from baseline to month 30; however, the increase was smaller for the pooled tafamidis group compared with placebo (least squares mean change from baseline, 1,771.7 pg/mL versus 3,947.7 pg/mL). In other exploratory analyses, smaller magnitudes of changes were observed for global longitudinal strain (GLS), left ventricular (LV) end diastolic interventricular septal wall thickness, LV posterior wall thickness, and left ventricular ejection fraction (LVEF) for the pooled tafamidis group compared with placebo.

Harms Results

Almost all patients experienced at least one AE (98.9% placebo, 98.3% tafamidis 80 mg, and 98.5% pooled tafamidis). Among the most common events were cardiac-related (i.e., atrial fibrillation: 18.6% placebo, 19.9% tafamidis 80 mg, and 19.3% pooled tafamidis; and cardiac failure: 33.9% placebo, 26.1% tafamidis 80 mg, and 28.8% pooled tafamidis). Gastrointestinal effects, such as constipation (16.9% placebo, 14.8% tafamidis 80 mg, and 15.2% pooled tafamidis), diarrhea (22.0% placebo, 12.5% tafamidis 80 mg, and 12.1% pooled tafamidis), and nausea (20.3% placebo, 11.4% tafamidis 80 mg, and 11.0% pooled tafamidis) were also common, but experienced by a lower percentage of patients who received tafamidis compared with placebo. At least one serious adverse event (SAE) was experienced by 79.1% in the placebo group, 75.6% in the tafamidis 80 mg group, and 75.4% in the pooled tafamidis group (Table 1). The most common SAEs were cardiac-

related (i.e., atrial fibrillation and cardiac failure) and condition-aggravated (32.8% placebo, 22.7% tafamidis 80 mg, and 23.1% pooled tafamidis). More patients in the placebo group stopped treatment due to AEs (29% placebo versus 23% tafamidis 80 mg, and 21% pooled tafamidis); however, withdrawal from the study due to AEs was similar for the placebo, tafamidis 80 mg, and the pooled tafamidis groups (6.2% versus 6.8% and 6.4%, respectively). In terms of notable harms, hypothyroidism was experienced by 5.6% in the placebo, 6.8% in the tafamidis 80 mg, and 6.4% in the pooled tafamidis group. More patients who received tafamidis had thyroxine abnormality below 0.8 of the lower limit of normal (4.5% of the placebo, 29.9% of the tafamidis 80 mg, and 23.9% of the pooled tafamidis group). Pruritis or rash occurred in more patients in the placebo group.

Table 1: Summary of Key Results From ATTR-ACT

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg[a] N = 176	Pooled tafamidis N = 264
All-cause mortality and CV-related hospitalization (month 30) (ITT set)			
Alive, n (%)	101 (57.1)	122 (69.3)	186 (70.5)
CV hospitalization, mean per year[b]	0.46	0.34	0.30
Finkelstein-Schoenfeld P value	Reference	0.0030	0.0006
Mortality (month 30)[a] (ITT set)			
Total deaths, n (%)	72 (40.7)	49 (27.8)	72 (27.3)
CV-related	50 (28.2)	36 (20.5)	53 (20.1)
Non–CV related	13 (7.3)	9 (5.1)	14 (5.3)
Indeterminate	9 (5.1)	4 (2.3)	5 (1.9)
All-cause mortality, HR (95% CI)[c]	Reference	0.69 (0.49 to 0.98)	0.70 (0.51 to 0.96)
CV-related mortality, HR (95% CI)[c]	Reference	0.69 (0.47 to 1.01)	0.69 (0.49 to 0.98)
Hospitalization (month 30)[a] (ITT set)			
Total hospitalized, n (%)	136 (76.8)	125 (71.0)	190 (72.0)
CV-related	107 (60.5)	96 (54.5)	138 (52.3)
Non–CV related	80 (45.2)	81 (46.0)	125 (47.3)
Indeterminate	0 (0)	2 (1.1)	3 (1.1)
All-cause hospitalization rate ratio (95% CI)[d]	Reference	NR	0.79 (0.69 to 0.91)
CV hospitalization rate ratio (95% CI)[d]	Reference	NR	0.68 (0.56 to 0.81)
KCCQ overall score (month 30) (ITT set)			
N	84	[redacted]	170
LS mean[e] change from baseline (SE), points	−20.8 (2.0)	−7.3 (1.5)	−7.2 (1.4)
LS mean difference (95% CI), points	Reference	[redacted]	13.7 (9.5 to 17.8)
P value	Reference	[redacted]	< 0.0001
6MWT (month 30) (ITT set)			
N	70	[redacted]	155
LS mean[e] change from baseline (SE), metres	−130.6 (9.8)	−54.8 (7.5)	−54.9 (5.1)
LS mean difference (95% CI), metres	Reference	[redacted]	75.7 (57.6 to 93.8)
P value	Reference	[redacted]	< 0.0001
NT-proBNP (month 30)[a] (ITT set)			
N	80	NR	170
LS mean[e] change from baseline (SE), pg/mL	3,947.7 (507.4)	NR	1,771.7 (306.1)
LS mean difference (95% CI), pg/mL	Reference	NR	−2,176.0 (−3,319.4 to −1,032.6)
P value	Reference	NR	0.0002

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg[a] N = 176	Pooled tafamidis N = 264
Patients with ≥ 1 SAE (safety set)			
n (%)	140 (79.1)	133 (75.6)	199 (75.4)
WDAE (safety set)			
Discontinued treatment, n (%)	51 (28.8)	40 (22.7)	56 (21.2)
Discontinued study, n (%)	11 (6.2)	12 (6.8)	17 (6.4)
Notable harms (safety set)			
Hypothyroidism, n (%)	10 (5.6)	12 (6.8)	17 (6.4)
Thyroxine abnormality < 0.8 LLN, n/N (%)	7/157 (4.5)	47/157 (29.9)	57/238 (23.9)
Pruritis, n (%)	15 (8.5)	12 (6.8)	16 (6.1)
Rash, n (%)	12 (6.8)	6 (3.4)	9 (3.4)

6MWT = six-minute walk test; ANCOVA = analysis of covariance; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; ITT = intention to treat; LLN = lower limit of normal; LS = least squares; MMRM = mixed model with repeated measures; NR = not reported; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; SE = standard error; TTR = transthyretin; WDAE = withdrawal due to adverse event.

[a] Exploratory analysis.

[b] Among patients alive at month 30. CV-related hospitalizations per year is calculated as patient's number of CV-related hospitalizations divided by duration on study in years.

[c] From a Cox proportional hazards model with TTR genotype (wild-type and variant) and NYHA baseline classification (class I and II combined and class III) in the model.

[d] From a Poisson regression, with treatment, TTR genotype (wild-type or hereditary), NYHA baseline classification (class I and II combined and class III), treatment by TTR genotype interaction, treatment by NYHA baseline classification interaction, and treatment duration.

[e] LS mean is from an MMRM ANCOVA model with random effects of the study centre and the patient; fixed effects of treatment, visit, TTR genotype (wild-type and variant), and visit by treatment interaction; and covariate of baseline score.

Source: Clinical Study Report for ATTR-ACT.[7]

Critical Appraisal

There were slight imbalances in baseline NT-proBNP level and NYHA class III, where patients randomized to placebo had higher NT-proBNP and more patients were in class III. This suggests that some patients in the placebo group may have had more severe cardiomyopathy. However, these slight differences in NT-proBNP and NYHA class III would likely not have a major impact on the results for mortality between tafamidis and placebo.

The 30-month study was completed by 48% of patients in the placebo group, 64% in the tafamidis 80 mg group, and 65.5% in the tafamidis pooled group. More patients in the placebo group discontinued from treatment (52% in the placebo group versus 36% in the tafamidis 80 mg group and 34.5% in the tafamidis pooled group). The main reason for discontinuation was death, which was higher in the placebo group (21.5% versus 14% and 15%, respectively). Although a large percentage of patients did not complete the trial due to death and withdrawal of consent, all patients who were randomized were rigorously followed up to determine vital status and transplantation and CMAD implantation status for the primary outcome of all-cause mortality.

Nonetheless, due to the large number of patients who did not complete the trial, there was a considerable amount of missing data for the key secondary and exploratory outcomes. No imputation of missing data was conducted, although a pattern mixture analysis was carried out for the KCCQ and 6MWT that included the pattern of missing data in the mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) models, and which yielded results that were similar to the main analyses.

Prohibited medications included calcium channel blockers, digitalis, diflunisal, and certain other nonsteroidal anti-inflammatory drugs (NSAIDs). Many patients were found to be using prohibited medication (especially calcium channel blockers, which were used by about 6% of patients on placebo and 8% of patients on tafamidis 80 mg). The data for these patients were still incorporated into efficacy and safety analyses, as it was deemed that they did not present with any SAEs due to the use of the prohibited medications; patients using prohibited medications were required to discontinue these medications after they were identified, but not required to discontinue from the study.

The patients in the trial were elderly, with the majority being male and white. Patients with NYHA classes I to III were included, with less than 10% in class I, about 60% in class II, and about 30% in class III. About 75% of patients had wATTR-CM and 25% had hATTR-CM, with the most common mutation being V142I or V122I. The clinical experts consulted for this review indicated that the patient characteristics were representative of the patients they see in clinical practice, although a larger percentage (close to 90%) will have wATTR-CM. Patients with NYHA class IV or previous heart/liver transplant were excluded and, therefore, the results cannot be applied to these patient populations. The clinical experts indicated that patients with NYHA class IV are not anticipated to benefit from treatment with tafamidis and that only a small proportion of patients with ATTR-CM undergo heart transplantation in Canada.

The primary analysis was done on the pooled tafamidis group versus placebo, whereas the dose of interest based on the Health Canada indication is tafamidis 80 mg. All analyses based on the 80 mg dose were exploratory and, therefore, statistical conclusions for the 80 mg dose cannot be made directly. The pooled group contained one-third of the patients taking tafamidis 20 mg and, in general, the results on the primary outcomes were consistent between the pooled and 80 mg group.

Indirect Evidence

No indirect evidence was submitted by the sponsor. An independent literature search was conducted for indirect evidence by CADTH, but no studies were identified that met the inclusion criteria of the CADTH Common Drug Review (CDR) review protocol.

Other Relevant Evidence

The long-term open-label extension study (NCT02791230) for tafamidis is ongoing. The sponsor provided additional information to CADTH during the review process from an interim analysis for the ongoing extension study. These data suggest that treatment with tafamidis may offer a survival benefit compared with placebo, but this conclusion is speculative due to the paucity of methodological detail available to assess the validity of these results. In the absence of more compelling long-term data, the durability of the treatment effect beyond 30 months remains inconclusive.

Conclusions

Based on a single double-blind, phase III RCT in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis was associated with reduced mortality and hospitalizations after 30 months compared with placebo. Clinically important differences were also observed in favour of tafamidis at month 30 in HRQoL and disability progression, as measured by the KCCQ overall score and 6MWT, respectively. Exploratory subgroup analyses suggested that treatment benefits are present for wATTR-CM, hATTR-CM, NYHA class I/II, and NYHA class III, although the benefits for patients in NYHA class III are less clear. The most common AEs were cardiac-related (i.e., atrial fibrillation and cardiac failure). The most common SAEs were cardiac-related or aggravation of condition and were experienced by a similar proportion of patients in the tafamidis and placebo groups. Thyroxine abnormality was higher in the tafamidis group, although this was anticipated to be of limited clinical significance. Further, the clinical experts consulted for this review agreed that tafamidis appears to be fairly well tolerated and monitoring requirements are anticipated to be minimal.

The current management strategy for ATTR-CM is primarily supportive cardiac disease treatments, as there are very few options available that target the underlying disease process. The only other TTR stabilizer used for the treatment of ATTR-CM in Canada is diflunisal; however, this is used beyond the Health Canada indication in this patient population, is associated with numerous limitations, and is not supported by rigorous evidence. There is no comparative evidence for tafamidis versus diflunisal; however, the clinical experts consulted for this review acknowledged that tafamidis appears to meet an unmet need for patients with wild-type and hereditary ATTR-CM.

Introduction

Disease Background

ATTR-CM is a life-threatening, progressive disease that occurs in hereditary and wild-type forms. ATTR-CM occurs when TTR amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure and, ultimately, death.[1,2,3] Symptoms of ATTR-CM are typical of restrictive cardiac disease and include dyspnea on exertion, orthostatic hypotension, and syncope, as well as conduction abnormalities, including bundle branch block, atrioventricular block, sinoatrial block, and atrial fibrillation.[4,5] The mean progression to death for patients with ATTR-CM is within two to three years (median survival, 25.6 months) of diagnosis for the hereditary form and up to five years (median survival, 43.0 months) for the wild-type form,[8] with most patients dying from cardiac causes, including sudden death, congestive heart failure, and myocardial infarction.[1,2]

Many of the manifestations of ATTR-CM are common with advancing age and not specific to ATTR-CM. As a result, ATTR-CM is often diagnosed only in later phases of disease when there is significant myocardial amyloid deposition and advanced restrictive cardiomyopathy. ATTR-CM is commonly underdiagnosed, as a definitive diagnosis occurs via histological confirmation of myocardial ATTR deposition through invasive cardiac biopsy.[9] As cardiac biopsy is associated with a risk of fatal cardiac complications,[10] the application of non-invasive imaging with nuclear scintigraphy has been used in the diagnostic pathway for patients with ATTR-CM.[10-12] Objective measures of cardiac involvement include abnormal electrocardiogram, left and right ventricular wall thickening by echocardiogram, and elevated cardiac biomarkers such as NT-proBNP.[4,5] These electrocardiogram, echocardiogram, and laboratory test findings are non-specific for heart failure, making the diagnosis of cardiac amyloidosis difficult and likely resulting in under diagnosis of this condition.[13]

The hereditary form is caused by genetic mutations that destabilize the TTR protein, which is produced predominantly in the liver and transports thyroxine and vitamin A in plasma.[14] The natural state of the TTR protein is a tetramer; however, gene mutations can cause the protein to disassociate, misfold, and aggregate into amyloid fibrils that are deposited into various tissues in the body. More than 120 mutations of the TTR gene have been identified that produce various phenotypic presentations.[15] The mutation that is most commonly associated with cardiomyopathy is V122I, but has low penetrance.[15,16] The V30M mutation is most common outside of the US and causes a predominantly polyneuropathic manifestation, although it may also result in cardiomyopathy.[15] The wild-type form of TTR is not associated with genetic mutations. It may result in amyloid deposits in tissues, causing an age-related amyloidosis, also known as senile systemic amyloidosis, that primarily affects men aged 60 years and older (later than hereditary forms).[14] An autopsy study (N = 85) found that amyloid deposits were present in 25% of patients older than 85 years of age, although the clinical relevance of these deposits is unknown, as disease likely results only with severe and widespread infiltration.[15] Clinically significant cardiac TTR amyloid may occur in 8% to 16% of people over 80 years of age.[17] According to the clinical experts consulted by CADTH for this review, the prevalence of wild-type or hereditary AATR-CM is unknown in Canada.

Standards of Therapy

Treatment options that address the underlying disease process of ATTR-CM are limited. Both wATTR-CM and hATTR-CM are treated in a similar manner. Diflunisal is an NSAID that has been used as a TTR stabilizer, but there is limited evidence to support its use for ATTR-CM and it is not approved for this use in Canada.[15] This drug also has a number of side effects that limit its use, particularly in patients with heart failure or renal impairment, which is common in ATTR-CM. Side effects include gastrointestinal ulceration and bleeding, altered renal function, renal decomposition, fluid retention, and precipitation of congestive heart failure.[18] Heart or combined heart and liver transplantation is an option for hATTR-CM in younger patients (< 50 years); however, transplantation is associated with several complications, such as lack of donors, need for lifelong immunosuppression, and exclusion of older patients or those with advanced disease.[15] Experimental treatments for ATTR-CM include doxycycline plus tauroursodeoxycholic acid in combination, or green tea extract (epigallocatechin-3-gallate [EGCG]). According to the clinical experts consulted by CADTH for this review, these treatments are rarely used in clinical practice and only by a few clinicians.[15] Supportive treatments for cardiac disease (i.e., standard medications for arrhythmias or heart failure, such as diuretics) are important for the management of ATTR-CM. However, according to the clinical experts, supportive treatments are not as effective in patients with ATTR-CM and are associated with harms; therefore, the management of cardiac disease in this patient population is difficult.

Drug

Tafamidis meglumine is a small molecule that stabilizes the TTR protein in both the wild-type and hereditary forms of the disease. The indication is for the treatment of adult patients with cardiomyopathy due to ATTR, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.[6] Tafamidis is available as a 20 mg capsule that is taken orally. The recommended dose of tafamidis meglumine is 80 mg (administered as four 20 mg capsules) taken orally once daily, with or without food. In this report, tafamidis refers to tafamidis meglumine.

The European Medicines Agency has approved tafamidis 20 mg once daily for the treatment of TTR amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.[19] The FDA approved tafamidis meglumine 80 mg and tafamidis 61 mg once daily (which is equivalent to tafamidis meglumine 80 mg) as a treatment for ATTR-CM.[20]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the CORD with support from the CASN, provided input for this review.

CORD is Canada's national network for organizations representing patients with rare disorders. CORD provides a strong common voice to advocate for health policy and a health care system that works for those with these conditions. CORD works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for all rare disorders in Canada. The CASN is a not-for-profit, all-volunteer organization, formed by patients with amyloidosis and their family members. The CASN offers a toll-free helpline, an educational website, and a support community connected through social media and meetings.

CORD and CASN did not receive any direct help in writing this submission. There was no external assistance with data collection or analysis for this submission. CORD declared receiving funding (in the range of $10,001 to $50,000 over the past two years) from Pfizer Canada Inc., the sponsor of the tafamidis submission to CADTH.

2. Condition-Related Information

CORD/CASN gathered information for this submission through an online survey (N = 42) and individual patient interviews (N = 4). Participants in the survey and interview were recruited from the US-based network, Amyloidosis Support Groups, Inc., which has support groups in more than 35 US cities as well as global patient engagement including CASN. In addition, two Canadian clinicians treating patients with amyloidosis, as part of expanded tafamidis trials, agreed to approach patients who could be interviewed for the submission process. Participants included patients who were diagnosed with or suspected of having ATTR-CM, either inherited or wild-type and their caregivers. Among the 42 online respondents, 45% identified as a person diagnosed with wild-type ATTR-CM (wATTR-CM); 26% were diagnosed with hATTR-CM; and another 5% had symptoms consistent with ATTR-CM but had no confirmed diagnosis. Another 2% (N = 1) reported a very rare type of ATTR-CM that included both hereditary and wild-type, and 2% (N = 1) reported that they had not received a confirmatory diagnosis. Among respondents, 19% (8 individuals) were caregivers. The majority of patients (66%) were diagnosed when they were between the ages of 60 and 79 (ages ranged from 20 years to 79 years). The duration since patients were diagnosed with ATTR-CM ranged from less than one year (24%) to greater than five years (up to 10 years, 3%). Most of the patients represented in the survey identified as male (87%) and 11% as female (< 2% not identified). Among those who specified a country of residence (N = 38), 50% were in the US, 45% in Canada, and 5% elsewhere (Australia). For most questions, there were no notable differences between Canadian and other respondents, so this patient input combined information from all countries, except in a few instances where there were notable differences.

Almost all patients (or caregivers) reported that ATTR-CM was debilitating and interfered significantly with daily functioning and quality of life. Like all types of ATTR, the condition affects multiple systems in the body. Regarding the symptoms related to cardiac functioning (namely, shortness of breath), more than one-fourth (28%) reported these as "serious" or

"incapacitating," while about three-fifths (59%) reported these as "moderate." About one-fifth (22%) said symptoms of "swelling in feet, ankles, and legs" were "serious," but about one-half (51%) said these were experienced "never" or "infrequently." Other cardiac-related symptoms, specifically, palpitations, arrhythmia, and chest pain, were "serious" for one-fifth (21%), while nearly half (48%) said these were "never" or "infrequently" experienced. Neuropathy was reported as moderate by 28% of respondents and not a problem by 14%. Finally, impact on cognitive functioning (e.g., confusion, headaches, trouble thinking) was less of an issue for most respondents, with about one-half to three-quarters reporting "no problem" or "never" experiencing these impacts. Some examples of the direct quotes are listed subsequently:

> "My husband with ATTR-CM was unable to do the normal day-to-day functions, such as getting dressed, tying up shoes, going up stairs… changing light bulbs, any yard work, auto repairs, going to the store, etc."
>
> "(The impact on me is significant) my capacity for exertion is approximately 50% of what it was; I was no longer able to retain a career that included a heavy travel schedule and long working hours; I experienced a forced retirement long before I was mentally ready or prepared to accept the necessary adjustments required when in retirement."
>
> "I was an airline captain; this diagnosis ended my career as I could no longer hold a medical for my license. Financially the impact has been huge ending my career 9 years early. I have been slowly losing the physical capacity to do almost all the physical activities…"
>
> "The fear of living with a fatal disease, no real time frame, with no potential cure in site, is devastating to the whole family. Causes a rollercoaster of emotions for all."
>
> "…I find myself wanting to with draw from a situation because of a need to rest, this causes me to become withdrawn and depressed.… without the research program that supplies the medicine free it would/could be a great burden causing a lot of stress to myself and family."
>
> "After 3 years of in and out of hospitals defibrillator, dobutamine IV pump, several cardio ablations and episodes of atrial fibrillation, I had to get a heart and liver transplant A roller coaster ride ever since…"

3. Current Therapy-Related Information

The patient group mentioned that, prior to tafamidis, there have been no therapies specific to ATTR-CM. Almost all patients (86%) did report receiving treatment to manage symptoms related to organ damage, namely, heart damage, nerve damage, and inflammation. However, among Canadians, 71% said they received some treatment (not including tafamidis), while 29% had not. The therapy reported as used by most respondents currently (67%) included either medicines to manage fluid and/or mineral levels (e.g., electrolytes, mineral and vitamin supplements), with 13% reporting previous use. About half (50% to 54%) were currently taking some form of cardiac management therapy to manage blood pressure (e.g., diuretics) or regulate heartbeat (e.g., amiodarone), or taking blood thinners (e.g., warfarin) to minimize clots, with about 8% to 25% taking one or more of these cardiac therapies in the past. Diflunisal, an NSAID, was currently being used by about one-third, with one-third having taken it in the past, and one-third reporting no usage. A small number of respondents reported taking antibacterial treatments or home therapies, including green

tea extract and other medicines to manage gastrointestinal distress. Given that the liver is the site of TTR production, liver transplantation was once considered a routine or "standardized" curative or life-extending option. However, longer-term evidence indicated that symptoms often reoccurred and it was not recommended or accessible to all ATTR patients. Only two respondents indicated receiving a liver transplant: one of them resided in Canada and the other was in the US. In addition, three respondents from the US reported they were in a clinical trial using AG10, a small molecule designed to potently stabilize tetrameric TTR.

Respondents were asked to rate the effectiveness of each therapy in managing ATTR-CM symptoms on a five-point scale anchored by "not at all" to "very well." Patients from the US reported the current therapy was "not at all" effective. In terms of those with a liver transplant, patients reported that outcomes were "not at all" or "somewhat" effective in managing symptoms. Among those taking medication to manage their cardiac symptoms (e.g., diuretics, blood thinners), most (about 68%) reported that the therapies worked well or very well for keeping their cardiac symptoms under control (namely, blood pressure, arrhythmia, or blood clots). The remainder of patients reported that these therapies were "somewhat" effective, with 5% reporting they were "not at all" effective. Respondents reported similar ratings for treatments to manage fluid levels, with 68% saying they worked "well" or "very well" and about one-fourth (26%) saying they were "moderately" effective. Treatments to address inflammation (mainly diflunisal) were regarded less well, with two-thirds saying their effectiveness was "moderate" or "poor," while only one-third felt they worked well.

Among patients using patisiran (N = 4, all from the US), there was an even split between those reporting it was working "well/very well" and those who felt it worked "somewhat/poorly/not at all." For the one Canadian patient on inotersen, the response was "unsure" at this time.

Respondents were mostly pessimistic about the effectiveness of current treatment options. In response to the open-ended question, "Not including tafamidis (Vyndamax and Vyndaqel), how effective are the available treatments for ATTR-CM?," most indicated that they felt their therapies had little or no effect on slowing or stopping disease progression. Examples of some direct quotes regarding the current treatment effectiveness are as follow:

> "Unknown. It's been difficult to diagnose the rate of progression of the wild-type ATTR cardiac amyloidosis, or to get any real sense of the prognosis of this disease for me."
>
> "They are somewhat ineffective."
>
> "Prior to being started on the open label drug trial for Tafamidis, I was given doxycycline and Ursodiol. I suffered very few side effects from that but seemed to need more BP control measures and more periodic use of diuretics."
>
> "They appear to maintain in a stable condition."
>
> "As far as we know there isn't any other effective treatment."

4. Experience and Expectations About the Drug Being Reviewed

Among all respondents, about 39% had received tafamidis. However, among Canadian respondents, 47% were receiving tafamidis. Respondents were asked about the benefits of tafamidis, based on their experience and/or knowledge. The responses reflected both optimism and realism. The patient group reported two types of benefits. The first referenced the impact on symptoms, namely, a reduction in nerve pain, an increase in strength and

energy, better appetite, and improved mobility. The second related but distinct benefit was "slowing or halting" disease progression. Thus, in their day-to-day life, patients felt better and were able to do more. As importantly, they were optimistic that this insidious disease was being held in check, if not actually cured. Some direct quotes are listed subsequently:

> "I expect this drug to dramatically slow or perhaps even halt the progression of my disease. This would be wonderful… I have recently started the 3rd stage clinical trial of Tafamidis. I have not experienced any adverse side effects after 6 weeks on the trial…"

> "… At my age and condition, I hope that it will provide me with at least the level of life style I currently have and will in the future help other people to live a good life despite the health problems."

> "… hopefully buying the patient a better quality of life for a longer period."

Almost all participants receiving tafamidis reported they had experienced no side effects with the therapy (thus far). However, most said they have only been on therapy for a short time, so they also cannot really attest to the positive effects.

Some quotes are listed subsequently:

> "In my experience [6 months on Tafamidis 61 mg/ day] I have felt NO side effects."

> "No side effects to date...I have been on the drug for 6 months...61mg capsule, once per day."

When asked about the importance of tafamidis to individuals with ATTR-CM (hereditary or wild-type), they were unanimous in calling for availability to everyone, regardless of current disease status. Examples of some quotes are subsequently:

> "I can't stress enough about having access to a therapy such as tafamidis. Any chance to maintain and perhaps improve one's ability to function in a productive manner is critical. Having an opportunity to lengthen one's lifespan is obviously invaluable..."

> "Patients with ATTR amyloidosis with cardiac involvement have had no hope until recently."

> "This had been like a death sentence over the last several years. Now we have the possibility of a treatment, to perhaps stabilize and improve quality of life. It is imperative that this is approved and that these patients are given back some quality. It's been a long road."

> "…this drug offers hope where my understanding is that previously there was no known treatment for the disease."

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). In addition, as part of the tafamidis meglumine

review, a panel of three clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented subsequently.

Description of the Current Treatment Paradigm for the Disease

The current treatment paradigm for ATTR-CM is supportive care, which includes standard medications for heart failure, such as diuretics, and treatments for atrial fibrillation and other cardiac comorbidities. The standard treatments for heart failure, however, are not as effective in patients with ATTR-CM as in other patient populations. It is generally accepted that beta-blockers are poorly tolerated, and many patients with ATTR-CM do not tolerate angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. These therapies are also not effective, as the pathophysiology of ATTR-CM is not as dependent on neurohormonal activation as it is in other etiologies of heart failure. Digoxin binds to amyloid fibrils and can cause toxicity at normal serum levels. Calcium channel blockers (not used for heart failure per se, but often used in atrial fibrillation) also bind amyloid fibrils and can cause adverse heart failure outcomes.

Although the primary goal of treatment is to stabilize disease and prevent further progression, there is currently no treatment that specifically targets the TTR pathology of the condition. Diflunisal has been studied primarily in patients with hereditary ATTR with polyneuropathy (hATTR-PN) and is used beyond the Health Canada–approved indication in this patient population. There is also some evidence for its use in hereditary ATTR with cardiac involvement and in wild-type disease. Obtaining access to diflunisal for patients with ATTR-CM may be difficult and side effects may limit its use. Other off-label treatments are doxycycline in combination with ursodiol and green tea extract, but these are rarely used in clinical practice in Canada. Patisiran and inotersen are approved for hATTR-PN, but also have some data pertaining to cardiac outcomes. However, there is limited evidence of any survival benefit with the available disease-modifying therapies. Tafamidis is expected to modify disease, with potential to stabilize disease progression. It is currently available through Health Canada's Special Access Programme, compassionate use, and through an open-label extension study which is currently ongoing, with a few sites in Canada.

Heart transplant or combined liver-heart transplant may be considered for a highly selective group of patients with advanced heart failure (i.e., significant disease burden to justify transplant, but not advanced to such a degree that would contradict a transplant), and with no other comorbidities. It is more likely to be an option for younger patients with hATTR-CM, given the advanced age of patients with wATTR-CM in whom the transplantation procedure is associated with safety concerns. After transplant, TTR deposition may still occur; however, it is unclear if these patients should receive additional treatment. It is unlikely that patients with wATTR-CM, who have undergone transplant, would require additional treatments due to their advanced age and the unlikely possibility of developing clinically relevant amyloid deposits in the new organ within their lifetimes.

Diagnosis

Amyloidosis is a rare disease that can be difficult to diagnose. The diagnosis of ATTR-CM must be confirmed via biopsy or scan (technetium pyrophosphate scan), and light-chain amyloidosis must be ruled out with mass spectrometry or urine/protein studies. Diagnostic testing is available in most academic centres and biopsy is available in transplant centres. Wild-type ATTR may be underdiagnosed because patients may initially be seen by neurologists for symptoms of carpal tunnel syndrome and a diagnosis of ATTR may not be considered. Further, the cardiac presentation is non-specific; atrial fibrillation, heart failure, and aortic stenosis are very common in patients without ATTR as well.

Treatment Goals

An ideal treatment would reverse disease progression but, more realistically, stabilize or slow disease progression. In this respect, the hereditary and wild-type forms of disease differ. Hereditary ATTR-CM is more prone to TTR deposition, presents earlier in life, and is more rapidly progressive, than wATTR-CM. The gene mutation, along with other factors, determine the disease course of hATTR-CM. In both hereditary and wild-type ATTR, there is wide variability in the rate of disease progression. An ideal treatment would also prolong life, reduce hospitalization, improve symptoms, improve quality of life, and provide hope to patients. For patients with combined cardiomyopathy and polyneuropathy, an additional goal of importance is to improve pain and mobility symptoms.

Unmet Needs

The primary unmet need is for disease-modifying treatments that address the underlying pathology of ATTR-CM. There is no treatment currently available that is supported by robust evidence for hereditary ATTR with pure cardiomyopathy phenotype or for any wild-type ATTR disease. The currently available treatments (e.g., diflunisal) lack evidence, are limited by side effects, and none are known to reverse, or stabilize, disease.

Place in Therapy

Tafamidis is expected to shift the current treatment paradigm for ATTR-CM and would be considered as a first-line treatment for eligible patients. Treatment should be started at earlier stages of disease. There are no other treatments for ATTR-CM with complementary mechanisms of action, to which tafamidis would be added. Patisiran and inotersen are two drugs used for hATTR-PN with different mechanisms of action from tafamidis. Theoretically, these drugs could potentially be used in combination but there is no evidence available to provide guidance on such decisions. Combination therapies may be considered by some clinicians in clinical practice for selected patients.

It would not be appropriate to recommend that patients with ATTR-CM try other treatments before initiating tafamidis because none of the other treatment are supported by evidence. If patients have hATTR-PN, then they could potentially be started on patisiran or inotersen.

Patient Population

All patients with ATTR-CM have a great unmet need for disease-modifying interventions. It is anticipated that patients who will benefit the most from treatment will be those with less advanced disease. However, treatment with tafamidis may also benefit patients with more severe disease (i.e., NYHA class III) in addition to NYHA class I and II with respect to disease stabilization. In sum, patients in NYHA classes I to III are likely to derive benefit of

treatment. Stage of disease is most commonly assessed using the NYHA functional classification combined with clinical judgment. With each higher NYHA class, the disease becomes more symptomatic.

It is unclear if patients with hATTR-CM who are pre-symptomatic (i.e., gene mutation identified but no presentation of symptoms) would be suitable for treatment with tafamidis. If the gene was known to be fully penetrant (such as the V30M), then mechanistically it would be appropriate to treat pre-symptomatic patients, although no evidence is available. For mutations with incomplete penetrance (such as V122I), treatment is more difficult to justify. Most clinicians would likely monitor these patients with diagnostic tests for early amyloid deposition and consider starting therapy once this was shown, regardless whether the patient is symptomatic or asymptomatic. Patients with wild-type ATTR-CM generally present with symptoms, but there are some patients who may be diagnosed by echocardiogram when minimally symptomatic. Patients who are asymptomatic, but with an established diagnosis of ATTR and clear cardiac involvement, should be treated.

Patients with end-stage or advanced disease (i.e., NYHA class IV) are least likely to benefit from treatment with tafamidis. Given that treatment benefit is not observed prior to six months, tafamidis may have limited usefulness in patients with short life expectancy (i.e., fewer than six or 18 months). Patients who do not wish to prolong life due to impaired quality of life are not suitable candidates for treatment. Other first-line treatments are approved for hATTR-PN and, therefore, tafamidis may not be suitable for these patients. Patients with a prior liver and/or heart transplant may have recurrence of disease, and it is unknown if these patients would benefit from treatment, although as previously mentioned, it is unlikely that such patients would require additional treatments.

Assessing Response to Treatment

In clinical practice, a subjective assessment of patients' symptoms and NYHA functional class (severity of heart failure symptoms and exercise tolerance) would be used to determine if a patient is responding to treatment. The cardiac biomarker NT-proBNP may be used in conjunction with other clinical factors, although it would not be used alone as an indicator of response. Echocardiogram parameters, such as LV wall thickness, may also be considered as an adjunctive assessment. It may be difficult to determine if a patient is responding because the treatment is meant to stabilize, but not improve, disease; the disease trajectory of a patient without treatment cannot be easily predicted. Also, since progression can be slow for patients with wATTR-CM, any benefits of treatment, especially concerning mortality, will take time to become evident.

A clinically meaningful response to treatment would be the absence of any disease progression or disease stabilization (i.e., patients whose disease status is the same as when they first presented in clinic). Variability among physician assessments is expected. Response would be based on clinical assessment (e.g., what activity tolerance can be achieved, can patient walk a block, can patient climb a flight of stairs and how many). These are typical questions that would be assessed in clinical practice. Other symptoms include swelling (for heart failure) and overall energy level. The NT-proBNP level should remain approximately stable as the baseline value. There is no defined magnitude of decrease for NT-proBNP that is considered clinically meaningful. Although a disease staging system for ATTR-CM has been suggested by Gillmore et al.,[21] this staging system is not widely used (even by those in the amyloid community) and it was not used in the pivotal tafamidis trial (ATTR-ACT); therefore, it is not clear how it would be used to make decisions regarding tafamidis treatment.

In the early stages of disease, response to treatment should be assessed every six months, but as patients develop heart failure, they will need to be assessed more frequently; the frequency of assessment will vary with disease severity. This will likely not differ between patients with hereditary and wild-type ATTR. Assessments should be individualized for each patient regardless of TTR status.

Discontinuing Treatment

Aside from AEs, there is no anticipated clear indication to stop treatment with tafamidis. It is expected that tafamidis will be a lifelong treatment, even in patients who have been on the drug for some time and have experienced disease progression. If a patient progresses from NYHA class III to class IV, the decision to continue or stop treatment would be made on a case-by-case basis. It may be reasonable to start to downgrade treatment at this point; however, it appears that tafamidis has fairly good tolerability and thus it is not expected that treatment would be discontinued for this reason. The transition from NYHA class III to class IV is also gradual, so it may take time to confirm whether the patient has truly progressed. Treatment discontinuation may lead to faster disease progression and, ultimately, impact survival. It is unclear if patients should stop tafamidis after being put on another drug (such as patisiran or inotersen), as there is no evidence available for combination therapies. If it appears that a patient would benefit from combination therapy with other drugs approved to treat ATTR, the decision as to which drug to use will likely be dependent on considerations of funding and access. It is expected that a multidisciplinary team involved in caring for the patient will collaborate to determine which of the indicated medications would provide the most benefit.

Prescribing Conditions

Patients with ATTR-CM are often referred to larger, tertiary care academic centres because these patients require multidisciplinary assessment and tafamidis would most likely be used in these settings. Tafamidis is an easy drug to use; it is administered orally once a day and not much monitoring for AEs is required. It could be prescribed in the community setting, primarily by cardiologists. Guidelines and education about its use would be needed for community settings. This would be especially important for patients in rural areas, who may not have access to tertiary care or academic centres.

Cardiologists will diagnose, initiate treatment, and monitor patients with ATTR-CM. Patients may also be monitored by internists. An assessment by a neurologist should also be done to exclude significant neurologic involvement in patients with hATTR-CM. In patients with wATTR-CM, a targeted referral to a neurologist should be made for patients with neurologic symptoms. Other specialties may also be involved, such as geriatricians, internal medicine specialists, and hematologists. Hematologists may be involved in distinguishing between TTR type and light-chain amyloidosis, but it is unlikely they would be prescribing tafamidis.

Clinical Evidence

The clinical evidence included in this review of tafamidis is presented in three sections. The first section is the systematic review, which includes pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section is intended to include indirect evidence; however, no indirect evidence was submitted by the sponsor, nor was any indirect evidence that met the selection criteria specified in the review identified from the literature. The third section is intended to include sponsor-submitted long-term extension

studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review. A long-term open-label extension study for tafamidis is ongoing and no data are currently available. No other studies included in the sponsor's submission were considered of relevance to this review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of tafamidis meglumine 80 mg (available as 20 mg oral capsules) for the treatment of adult patients with cardiomyopathy due to ATTR, wild-type or hereditary, to reduce all-cause mortality and cardiovascular-related hospitalization.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 2.

This systematic review protocol was established prior to Health Canada granting a Notice of Compliance for tafamidis.

Table 2: Inclusion Criteria for the Systematic Review

Patient population	Adults with cardiomyopathy due to wild-type or hereditary ATTR Subgroups: • Wild-type versus hereditary ATTR • Presence of mutations associated with cardiomyopathy (i.e., Val122Ile) versus absence of these mutations • Patients with previous heart or liver transplant versus no previous transplant • NYHA class
Intervention	Tafamidis meglumine 80 mg once daily
Comparators	• Diflunisal[a] • Supportive care[b] • Placebo
Outcomes	**Efficacy outcomes:** • Overall survival • Cardiovascular and all-cause mortality • Cardiovascular and all-cause hospitalization • Health-related quality of life[c] • NYHA class • Disability (e.g., six-minute walk test)[c] • Cardiac biomarkers: NT-proBNP and troponin I • Echocardiogram parameters (e.g., end diastolic interventricular septal wall thickness, LV posterior wall thickness, LVEF, global longitudinal strain) • Nutritional status (e.g., mBMI) • Need for heart or liver transplant • Need for cardiac device implantation **Harms outcomes:** AEs, SAEs, WDAEs, hypersensitivity, thyroxine level, thyroid dysfunction, vitamin A deficiency

Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; ATTR = transthyretin-mediated amyloidosis; LV = left ventricular; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Not approved by Health Canada for the indication under review.

[b] Supportive care may include treatment with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers.

[c] Outcomes of importance to patients, as identified in the patient input summary.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (www.cadth.ca/resources/finding-evidence/press).[22]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tafamidis. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Where possible, retrieval was limited to the human population. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 1, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on November 20, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (www.cadth.ca/grey-matters):[23] health technology assessment (HTA) agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials registries, and databases (free). google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 3. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

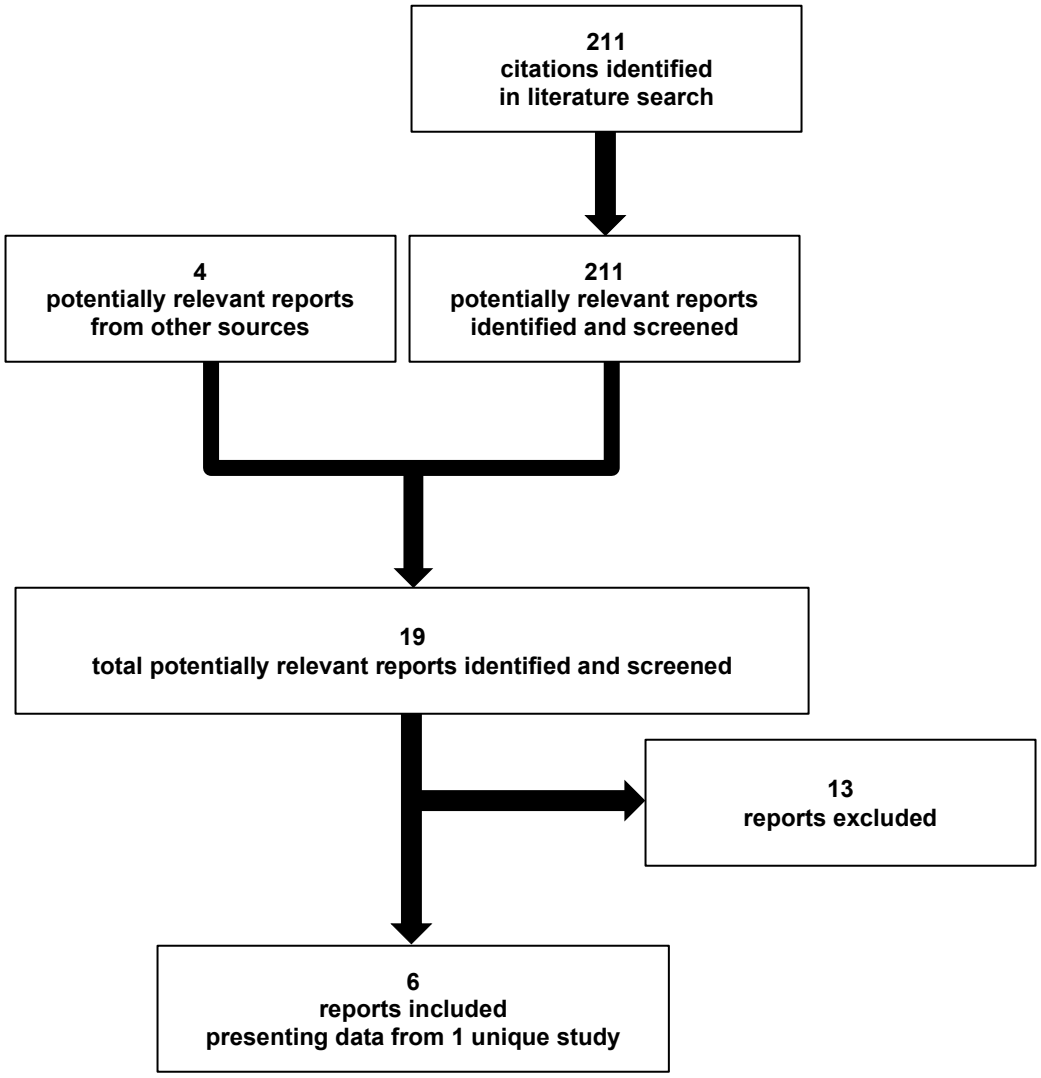


Table 3: Details of Included Studies

		ATTR-ACT
Designs and Populations	**Study design**	Multi-centre, placebo-controlled, DB, RCT
	Locations	Belgium, Brazil, Canada, Czech Republic, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, UK, and US (48 centres, 13 countries)
	Randomized (N)	441

	Inclusion criteria	• ≥ 18 and ≤ 90 years of age at time of randomization
		• Medical history of heart failure: at least one prior hospitalization for heart failure or clinical evidence of heart failure (volume overload or elevated intracardiac pressures) that required treatment with a diuretic
		• Documented TTR amyloid cardiomyopathy defined as either:
		  ○ wild-type TTR amyloid cardiomyopathy defined by all of the following: absence of a variant TTR genotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness > 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac); TTR precursor protein identified by immunohistochemistry, scintigraphy, or mass spectrometry, or
		  ○ hereditary TTR amyloid cardiomyopathy (required all of the following): presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness > 12 mm; and presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac)
		• Heart failure symptoms were optimally managed and clinically stable, with no cardiovascular-related hospitalizations within 2 weeks prior to baseline
		• Screening visit NT-proBNP ≥ 600 pg/mL
		• Able to complete > 100 m on the 6MWT at screening

	Exclusion criteria	• Echocardiogram assessment was not interpretable for measurement of wall thickness • Use of diflunisal and certain other NSAIDs not allowed by the protocol within 30 days prior to baseline[a] • mBMI < 600 kg/m^2*g/L • Taking tafamidis currently or previously • Require treatment with calcium channel blockers or digitalis • Diagnosis of primary light-chain amyloidosis • Prior liver or heart transplant, or implanted cardiac mechanical assist device • NYHA class IV at screening or baseline visit • History of sustained ventricular tachycardia or aborted ventricular fibrillation, or history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker was indicated but not placed • Heart failure due to ischemic heart disease (e.g., myocardial infarction) or uncorrected valvular disease and not primarily due to TTR amyloid cardiomyopathy • Known or suspected hepatitis B or C, HIV infection, or positive serology • Renal failure requiring dialysis and/or eGFR < 25 mL/min/1.73 m^2 • Urinary retention that required self-catheterization • Liver function tests > 2 times the upper limit of normal • Participation in studies of diflunisal, tauroursodeoxycholate, and doxycycline within 30 days before baseline • Pregnant or breastfeeding, or male patients with partners who were pregnant

		ATTR-ACT
Drugs	**Intervention**	Tafamidis meglumine 20 mg or 80 mg orally once daily
	Comparator(s)	Placebo
Duration	**Phase**	
	Run-in	None
	Double-blind	30 months
	Follow-up	None[b]
Outcomes	**Primary end point**	• All-cause mortality • Frequency of cardiovascular-related hospitalization
	Secondary and exploratory end points	**Key secondary:** • 6MWT • KCCQ **Other secondary:** • Cardiovascular-related mortality **Exploratory:** • All-cause hospitalization • EQ-5D-3L • Patient global assessment • 6MWT (change from baseline at time points other than month 30) • KCCQ (change from baseline at time points other than month 30) • NYHA classification • mBMI • NT-proBNP • Select echocardiogram parameters • TTR stabilization, TTR oligomer concentration, TTR concentration[b] • Diflunisal concentration[c]
Notes	**Publications**	Maurer 2017[24] Maurer 2018[25]

6MWT = six-minute walk test; ASA = acetylsalicylic acid; CDR = CADTH Common Drug Review; DB = double blind; eGFR = estimated glomerular filtration rate; EQ-5D-3L = EuroQol 5-Dimensions 5-levels; KCCQ = Kansas City Cardiomyopathy Questionnaire; mBMI = modified body mass index; NSAID = nonsteroidal anti-inflammatory drug; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; RCT = randomized controlled trial; TTR = transthyretin.

Note: Three additional reports were included (CDR submission package;[26] FDA medical review;[20] FDA statistical review[27]).

[a] The permitted NSAIDs were ASA, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

[b] Patients were to be treated for 30 months. For the purpose of this study, 30 months was defined as 910 days. For any patient who discontinued prior to 30 months, the site was to ensure a follow-up contact at month 30 (also called the follow-up period) to determine the patient's vital status and whether the patient had a heart and/or liver transplant or implantation of a cardiac mechanical assist device.[7]

[c] Outcome not assessed in this clinical report.

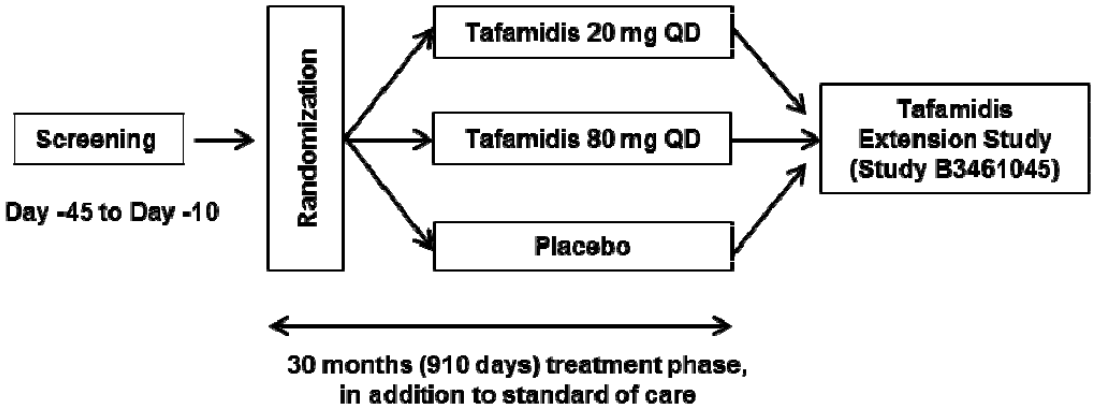
Source: Clinical Study Report for ATTR-ACT;[7] Maurer 2018.[25]

Description of Studies

One study was included in the CDR systematic review. ATTR-ACT (NCT01994889) was a multi-centre, phase III double-blind, placebo-controlled, RCT in adults with hereditary or wild-type ATTR-CM. It was completed in February 2018 across 48 centres in 13 countries, including one site in Canada and 25 sites in the US. A total of 441 patients were randomized in a 2:1:2 ratio to placebo (N = 177), tafamidis 20 mg (N = 88), or tafamidis 80 mg (N = 176) once daily for 30 months (Figure 2). Randomization was stratified by wild-type or hereditary ATTR-CM, and NYHA class I or class II/III. In the primary analysis, patients receiving the 20 mg or 80 mg dose of tafamidis were pooled, whereas exploratory analyses by dose group were conducted for the primary and key secondary outcomes. In the Health Canada product monograph for tafamidis, the dose indicated for ATTR-CM is 80 mg once daily, administered as four 20 mg capsules.[6] Therefore, the focus of this report is the tafamidis 80 mg treatment group; data for the pooled tafamidis dose group are also presented. Study visits occurred at three-month intervals, except for the initial week 2 and month 1 visits. After completion of the 30-month double-blind phase, patients were eligible to enter an open-label extension study (NCT02791230) to evaluate the long-term safety of tafamidis administered for 60 months.[28]

Patients were to be treated for 30 months. For the purpose of this study, 30 months was defined as 910 days. For any patients who discontinued prior to 30 months, the site was to ensure a follow-up contact at month 30 (also called the follow-up period) to determine the patient's vital status (death or alive) and whether the patient had a heart and/or liver transplant or implantation of a cardiac mechanical assist device.[7]

Figure 2: Study Design of ATTR-ACT



QD = once daily.

Source: Clinical Study Report for ATTR-ACT.[7]

Populations

Inclusion and Exclusion Criteria

Patients between the ages of 18 to 90, inclusive, with documented ATTR-CM and a medical history of heart failure were included in the trial. The ATTR-CM could be wild-type or hereditary, diagnosed by biopsy and/or scintigraphy to detect amyloid, and other factors as listed in Table 3. A medical history of heart failure was defined as at least one prior hospitalization for heart failure or clinical evidence of heart failure that required treatment with a diuretic. The heart failure symptoms were required to be clinically stable and patients must have been able to complete more than 100 metres on two six-minute walk tests (6MWT) conducted on different days (separated by a minimum of 24 hours and a maximum of two weeks) at screening. The NT-proBNP must have been at least 600 pg/mL at screening.

Patients were excluded if their mBMI was less than 600 kg/m^2*g/L or if they were NYHA class IV (i.e., unable to carry on any physical activity without discomfort, symptoms of heart failure at rest, and if any physical activity is undertaken, discomfort increases)[29] at the screening or baseline visit. Patients were also excluded if they had taken diflunisal or certain other NSAIDs 30 days prior to baseline, participated in trials of diflunisal, tauroursodeoxycholate, or doxycycline within 30 days prior to baseline, had ever taken tafamidis, required treatment with calcium channel blockers or digitalis, or had prior liver or heart transplant or an implanted CMAD. If during the study a patient chose to accept a donor organ transplant or had implantation of a CMAD, the patient was discontinued from the study prior to the operation. Patients with renal failure requiring dialysis or with an estimated glomerular filtration rate of less than 25 $mL/min/1.73m^2$ were excluded.

Baseline Characteristics

Table 4 presents the baseline characteristics for patients in the placebo, tafamidis 80 mg, and pooled tafamidis dose groups. Patients were elderly, with a mean age of 74.1 years in the placebo group and 75.2 years in the tafamidis 80 mg group. The majority of patients were male and white. The groups were balanced for BMI, although mBMI was slightly higher for placebo compared with tafamidis 80 mg and the pooled tafamidis group. The NT-proBNP level was slightly higher for placebo compared with the pooled tafamidis group, and more patients in the placebo group were in NYHA class III (35.6%) than were patients in the tafamidis 80 mg (31.3%) or pooled tafamidis (29.5%) groups. TTR status was well balanced across treatment groups: about 76% of enrolled patients had wild-type ATTR-CM and 24% had hATTR-CM. The most common mutations among patients with hATTR-CM were V142I or V122I (13% in the placebo group, 15.3% in the tafamidis 80 mg group, and 14.4% in the pooled tafamidis group).

Table 4: Summary of Baseline Characteristics (Intention-to-Treat Set)

	ATTR-ACT		
	Placebo (N = 177)	**Tafamidis 80 mg (N = 176)**	**Pooled tafamidis (N = 264)**
Age, years, mean (SD)	74.1 (6.7)	75.2 (7.2)	74.5 (7.2)
Age, years, range	51 to 89	46 to 88	46 to 88
Male, n (%)	157 (88.7)	158 (89.8)	241 (91.3)
Race, n (%)			
White	146 (82.5)	136 (77.3)	211 (79.9)
Black	26 (14.7)	26 (14.8)	37 (14.0)
Asian	5 (2.8)	11 (6.3)	13 (4.9)
Other	0 (0)	3 (1.7)	3 (1.1)
Time since diagnosis, years, mean (SD)	1.2 (1.4)	0.9 (1.2)	1.0 (1.3)
BMI (kg/m^2), mean (SD)	26.3 (4.3)	26.3 (3.8)	26.2 (3.8)
mBMI[a] (kg/m2*g/L), mean (SD)	1,066.4 (194.4)	1,064.5 (172.5)	1,058.8 (173.8)
NT-proBNP (pg/mL), median (IQR)	3,161.0 (1,864.4 to 4,825.0)	NR	2,995.9 (1,751.5 to 4,861.5)
NYHA class, n (%)			
Class I	13 (7.3)	16 (9.1)	24 (9.1)
Class II	101 (57.1)	105 (59.7)	162 (61.4)
Class III	63 (35.6)	55 (31.3)	78 (29.5)
Present medical history: At least one disease or syndrome, n (%)	173 (97.7)	176 (100)	264 (100)
Cardiac disorders	150 (84.7)	151 (85.8)	229 (86.7)
Peripheral neuropathy	16 (9.0)	20 (11.4)	28 (10.6)
Polyneuropathy	8 (4.5)	3 (1.7)	4 (1.5)
Wild-type ATTR-CM, n (%)	134 (75.7)	134 (76.1)	201 (76.1)
Hereditary ATTR-CM, n (%)	43 (24.3)	42 (23.9)	63 (23.9)
V142I/V122I	23 (13.0)	27 (15.3)	38 (14.4)
T80A/T60A	6 (3.4)	2 (1.1)	6 (2.3)
V50M/V30M	6 (3.4)	2 (1.1)	3 (1.1)
V40I/V20I	0 (0)	1 (0.6)	1 (0.4)
Other	8 (4.5)	10 (5.7)	15 (5.7)

ATTR-CM = transthyretin-mediated amyloidosis cardiomyopathy; BMI = body mass index; IQR = interquartile range; mBMI = modified body mass index; ITT = intention to treat; NR = not reported; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation.

[a] The mBMI was calculated by multiplying the BMI (weight [kg]) ÷ height [m^2]) by the serum albumin concentration (g/L).

Source: Clinical Study Report for ATTR-ACT;[7] Maurer 2018.[25]

Interventions

Patients were administered placebo, tafamidis meglumine 20 mg, or tafamidis meglumine 80 mg as soft gel capsules once daily for 30 months (910 days). The daily treatment was provided as four capsules per day, which consisted of either three capsules of matching blinded placebo and one capsule of blinded tafamidis 20 mg, four capsules of blinded tafamidis 20 mg, or four capsules of placebo. The capsules were swallowed with a glass of water at the same time in the morning. In some cases, patients were permitted to take the dose in the evening, prior to a clinic visit, to allow for pharmacokinetic sample collections. Missed doses were not replaced and patients resumed regular dosing the next day.

If a tolerability issue arose that was persistent and was anticipated by the investigator to impact adherence to treatment, but which did not impact patient safety, then the patient may have been reassigned to blinded treatment with a potential reduction in dose. For example, if a patient was receiving the 80 mg dose, then the dose may have been reduced to 40 mg. If a patient was receiving placebo or 20 mg, they would have been maintained on that dose but would receive a new container number to maintain blinding. If tolerability issues continued after reassignment, then patients may have been discontinued from treatment.

In addition to the main intervention, patients received standard of care such as diuretics. Medications that were considered standard of care were to be stabilized for at least four weeks prior to baseline. Doses of diuretics, however, could be changed within four weeks of baseline. Patients were permitted to use supplements and medications during the course of the study, except for drugs that were prohibited under the study protocol (i.e., diflunisal and certain other NSAIDs, digitalis, calcium channel blockers, tauroursodeoxycholate, and doxycycline). The NSAIDs that were permitted were ASA, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

Outcomes

The primary outcomes were all-cause mortality and frequency of cardiovascular-related hospitalization at month 30. Patients provided consent for the release of medical information to ensure that medical records could be accessed in the event that the patient could not be contacted at month 30. If the patient or designated contact could not be reached, then the patient's primary physician was contacted or appropriate national or regional registries were searched to ascertain vital status and whether the patient underwent heart transplantation or CMAD implantation. Patients who discontinued for transplantation (heart transplant or combined heart and liver transplant) or for implantation of a CMAD were handled as deaths in the primary analysis. All hospitalizations of patients until the time of discontinuation or completion of the study were reported to the end point adjudication committee. Hospitalization was defined as a non-elective admission to an acute care setting for medical therapy that resulted in at least a 24-hour stay. Cardiovascular-related hospitalization was defined as any hospitalization with a discharge diagnosis of a cardiovascular reason, such as heart failure, arrhythmia, myocardial infarction, transient ischemic attack, or stroke. For each hospitalization, one cause was assigned (i.e., cardiovascular or non-cardiovascular cause). In addition, hospitalizations adjudicated as indeterminate were included as cardiovascular-related.

Key secondary outcomes were the 6MWT and the KCCQ overall score. The 6MWT was conducted at screening, baseline, and at six-month intervals. The 6MWT is a commonly used test to evaluate the global function of organ systems involved in exercise, namely, the heart, lungs, peripheral circulation, blood, nervous system, muscles, and bones and joints during walking, a self-paced activity. The test was performed indoors along a flat, straight, enclosed corridor with a hard surface, with markings at every 3 metres. Observers of the test were trained and supervised prior to conducting the test alone. The MCID is 43 metres in patients with heart failure (Appendix 4). No minimal important differences (MIDs) were identified for patients with ATTR-CM.

The KCCQ is a 23-item, patient-completed questionnaire to assess health status and HRQoL in patients with heart failure. Sites were provided with approved translated versions of the KCCQ and patients completed the questionnaire at baseline and at six-month intervals. The KCCQ consists of eight domains (physical limitation, symptom stability,

symptom frequency, symptom burden, total symptoms, self-efficacy, quality of life, and social limitation), a clinical summary, and an overall summary score. The scores are transformed to a 0 to 100 range, with higher scores indicating better health status. The KCCQ is considered a reliable and valid self-report instrument for measuring disease-specific quality of life in chronic heart failure,[30-32] The KCCQ has been validated in patients with congestive heart failure with an MCID of 5.7 for the overall score (Appendix 4). However, no data were available for the validity or MCID of the KCCQ in patients with ATTR-CM.

An additional secondary outcome was cardiovascular-related death. All cases of death were reported to the end point adjudication committee, which reviewed each case and determined cause of death. Cardiovascular-related death included death due to heart failure, arrhythmia, myocardial infarction, sudden cardiac death, stroke, or other cardiovascular causes. In addition, deaths adjudicated as indeterminate were counted as cardiovascular-related.

Several exploratory end points were evaluated, including all-cause hospitalization, the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L), PGA, NYHA classification, mBMI, NT-proBNP, and echocardiogram parameters.

- The EQ-5D-3L was administered to patients after the KCCQ at baseline and then at six-month intervals. It is an instrument that is completed by the patient in two parts to assess generic HRQoL (Appendix 4). In the first part, patients rate their current health state on five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) on three levels (no problem, some problem, or extreme problem); in the second part, patients rate their current health state on an EuroQol 5-Dimensions Visual Analogue Scale (EQ VAS) with end points of worst imaginable health state (score of 0) to best imaginable health state (score of 100). Higher scores indicate a better health state. Although the EQ-5D-3L has been validated in several conditions, there is no information about its validity or MCID specifically in patients with ATTR-CM.
- The PGA was administered to patients after the KCCQ and EQ-5D-3L at baseline and then at six-month intervals. It is used to assess overall health status by asking patients to rate their current health based on seven options that range from “normal, not at all ill” to “among the most extremely ill.” Higher scores indicate better overall health. No data on the validity or MCID of the PGA were identified for ATTR-CM.
- The NYHA functional classification consists of four categories designed to assess the severity of heart failure. In ATTR-ACT, it was used to classify patients at baseline and then at six-month intervals, with class I to class IV defined as follows:

Class I: Patients with cardiac disease but without resulting limitations of physical activity (ordinary physical activity did not cause undue fatigue, palpitation, dyspnea, or anginal pain).

Class II: Patients with cardiac disease resulting in slight limitation of physical activity (comfortable at rest, but ordinary physical activity resulted in fatigue, palpitation, dyspnea, or angina pain).

Class III: Patients with cardiac disease resulting in marked limitation of physical activity (comfortable at rest, but less than ordinary physical activity caused fatigue, palpitation, dyspnea, or anginal pain).

Class IV: Patients with cardiac disease resulting in an inability to carry on any physical activity without discomfort (symptoms of cardiac insufficiency or of the anginal syndrome might be present even at rest and, if any physical activity was undertaken, discomfort was increased).

- The mBMI was calculated by multiplying the BMI by serum albumin.
- NT-proBNP was measured in blood by a central laboratory, with blood samples collected at screening, day 1, and months 12 and 30.
- Echocardiograms (2D Doppler) were performed at screening, and months 6, 18, and 30. The following outcomes were reviewed, as they were deemed to be the most clinically relevant by experts consulted for this review: GLS, LV end diastolic interventricular septal wall thickness, LV posterior wall thickness, and LVEF.

Harms included AEs, serious adverse events (SAEs), withdrawal due adverse events, deaths, and notable harms of hypersensitivity, hypothyroidism (including thyroxine level), and vitamin A deficiency. The period for the reporting of AEs was from the time a patient took at least one dose of the study drug until the patient's last visit. For SAEs, the time period began when a patient provided informed consent until and including 28 calendar days after the last dose of the study treatment.

Statistical Analysis

Power Calculation

The sample size was based on a treatment duration of 30 months, a two-sided significance level of 0.05, and assumptions of all-cause mortality rates of 12.5% for tafamidis and 25% for placebo (i.e., 50% reduction in mortality with treatment) and a frequency rate for cardiovascular-related hospitalization (number of hospitalizations per patient per year) of 1.5 for tafamidis and 2.5 for placebo, respectively. With these assumptions, 300 patients (120 for placebo, 60 for tafamidis 20 mg, and 120 for tafamidis 80 mg) would provide a power of more than 90% for the primary outcome.

Statistical Test or Model

In the primary analyses of the primary, key secondary, secondary, and exploratory outcomes, the 20 mg and 80 mg tafamidis groups (including patients who were reduced to 40 mg) were combined into a single tafamidis pooled group and compared with placebo. Exploratory analyses by dose group (i.e., 20 mg and 80 mg) were conducted for the primary, key secondary, and secondary outcomes.

The primary outcomes of all-cause mortality and cardiovascular-related hospitalization were analyzed using a hierarchical statistical testing approach and applying the Finkelstein-Schoenfeld method, with patients ranked on all-cause mortality first and then by cardiovascular-related hospitalization (if they could not be ranked by mortality). In this method, each patient was compared with every other patient within strata (i.e., wild-type or hereditary and NYHA class I/II combined or class III) in a pairwise fashion on all-cause mortality first, followed by cardiovascular-related hospitalization if patients could not be ranked based on mortality. All rankings were then combined to produce an overall test statistic. The null hypothesis was that neither all-cause mortality nor frequency of cardiovascular-related hospitalization were different between tafamidis and placebo. The alternative hypothesis was that at least one, or possibly both, outcomes (all-cause mortality and cardiovascular-related hospitalization) were different between tafamidis and placebo.

The time to event outcomes of all-cause mortality and cardiovascular-related mortality were also analyzed with Kaplan-Meier survival curves and Cox proportional hazard models with covariates of treatment, TTR genotype (wild-type or hereditary), and NYHA baseline classification (class I/II combined or class III). Cardiovascular-related days hospitalized and all-cause days hospitalized were analyzed with an analysis of variance (ANOVA) model with covariates of treatment, TTR genotype (wild-type or hereditary), NYHA baseline classification (class I/II combined or class III), treatment by TTR genotype interaction, and treatment by NYHA baseline classification interaction. The frequency of cardiovascular-related hospitalization and all-cause hospitalization was analyzed using a Poisson regression with treatment as covariate, TTR genotype (wild-type or hereditary), NYHA baseline classification (class I/II combined or class III), treatment by TTR genotype interaction, treatment by NYHA baseline classification interaction, and treatment duration.

The key secondary outcomes of change from baseline to month 30 in the 6MWT and KCCQ overall score were analyzed with an MMRM ANCOVA model that included the random effects of the study centre and patient within the centre; fixed effects of treatment, visit, TTR genotype (wild-type or hereditary), and visit by treatment interaction; and covariate of baseline score. A pre-specified hierarchical order for testing of the primary analysis and then key secondary end points, as indicated previously, was used to maintain the overall alpha at 0.05 for the primary analysis and the two key secondary end points. The multiplicity procedure was applied to the intention-to-treat (ITT) analysis set only. To maintain type I error at 0.05, statistical testing of the 6MWT and KCCQ were conducted only if the primary outcome (i.e., all-cause mortality and cardiovascular-related hospitalization) achieved statistical significance first. In addition, the 6MWT was tested first at the 0.05 level and, if statistically significant, then the KCCQ overall score was tested second. None of the other secondary or exploratory outcomes were adjusted for multiplicity.

Data Imputation Methods

If a patient did not return for a scheduled visit, the site made a minimum of three phone calls followed by a registered letter to inquire into the reason for the absence. Efforts were made to document patient outcomes, including vital status, heart transplantation, and implantation of CMAD through 30 months after the baseline visit. For patients who discontinued treatment or who withdrew from the study, a month 30 vital status follow-up was conducted to collect information on mortality, transplantation, and CMAD implantation. In the primary analysis based on the Finkelstein-Schoenfeld method, no imputation was done for missing cases. Also, no imputation of missing data was done for MMRM analyses of secondary and exploratory outcomes. A multiple imputation analysis using the method developed by Rubin[7] was applied only as an additional sensitivity analysis.

Subgroup Analyses

Exploratory subgroup analyses were conducted by TTR genotype (wild-type or hereditary) and NYHA baseline classification (class I/II combined and class III) for the primary, key secondary, and secondary outcomes.

Sensitivity Analyses

For the primary outcome analysis of all-cause mortality and cardiovascular-related hospitalization, three sensitivity analyses were conducted:

- using multiple imputation (method developed by Rubin[7]) to account for missing cases
- excluding hospitalizations adjudicated as indeterminate from the cardiovascular-related hospitalization outcomes
- excluding heart transplantation or implantation of CMAD from the all-cause mortality outcomes.

For the key secondary outcomes of 6MWT and KCCQ overall score, sensitivity analyses (termed pattern mixture analyses) were conducted that grouped patients based on the pattern of missing data. (Pattern 1A included patients who provided data for the key secondary outcomes at month 30. Pattern 1B included patients who had not provided data for key secondary outcomes at month 30.) The pattern mixture analysis used an MMRM ANCOVA model with an unstructured covariance matrix or (as appropriate): the study centre and the patient within the centre as random effects; treatment, visit, TTR genotype (variant and wild-type), pattern, visit by treatment interaction, and treatment by pattern interaction as fixed effects; and baseline score as covariate.[7]

Analysis Populations

The primary analysis for all outcomes was conducted on the ITT set, which was defined as all patients who were randomized, received at least one dose of the study drug, and who had at least one post-baseline efficacy evaluation. Supportive analyses were conducted in the per-protocol set, which included all patients in the ITT set who had no violations of inclusion/exclusion criteria and no major protocol violations. The safety analysis set included all patients who were randomized and who received at least one dose of the study drug.

Results

Patient Disposition

Of 548 patients screened, 441 (80.5%) were randomized to treatment with either placebo (N = 177), tafamidis 80 mg (N = 176), or tafamidis 20 mg (N = 88). Of the patients who were screened and not randomized (N = 107, 19.5%), 94 patients were not eligible for the trial, the most common reason being closure of enrolment for patients with wild-type ATTR. The remaining 13 patients were not randomized because they withdrew consent prior to randomization. Table 5 shows the patient disposition for the placebo, tafamidis 80 mg, and pooled tafamidis groups. All patients who were randomized were treated. The study was completed by 48% of patients in the placebo group, 64% in the tafamidis 80 mg group, and 65.5% in the pooled tafamidis group. More patients in the placebo group discontinued treatment (52% placebo versus 36% tafamidis 80 mg and 34.5% pooled tafamidis). The main reason for discontinuation was death, which was higher in the placebo group (21.5% versus 14% and 15%). Other common reasons were withdrawal of consent (21% versus 10% and 9.5%) and AEs (6.2% versus 6.8% and 6.4%) in the placebo, tafamidis 80 mg, and pooled tafamidis groups, respectively. The ITT and safety analysis sets included all patients who were randomized.

Table 5: Patient Disposition

	ATTR-ACT		
	Placebo	Tafamidis 80 mg	Pooled tafamidis
Screened, N	548		
Randomized, N (%)	441 (80.5)		
	177	176	264
Treated, N (%)	177 (100)	176 (100)	264 (100)
Completed, N (%)	85 (48.0)	113 (64.2)	173 (65.5)
Discontinued from study, N (%)	92 (52.0)	63 (35.8)	91 (34.5)
Reason for discontinuation, N (%)			
Death[a]	38 (21.5)	25 (14.2)	39 (14.8)
Wild-type	24/134 (17.9)	18/134 (13.4)	25/201 (12.4)
Hereditary	14/43 (32.6)	7/42 (16.7)	14/63 (22.2)
Withdrawal of consent	37 (20.9)	17 (9.7)	25 (9.5)
Adverse events	11 (6.2)	12 (6.8)	17 (6.4)
Organ transplant	5 (2.8)	5 (2.8)	6 (2.3)
CMAD implant	0 (0)	2 (1.1)	2 (0.8)
Protocol violation	1 (0.6)	1 (0.6)	1 (0.4)
Lost to follow-up	0 (0)	1 (0.6)	1 (0.4)
ITT, N	177	176	264
PP, N	169	171	255
Safety, N	177	176	264

CMAD = cardiac mechanical assist device; ITT = intention to treat; PP = per protocol.

[a] The number of deaths reported in this table refers to the number of deaths occurring during the study period.

Source: Clinical Study Report for ATTR-ACT.[7]

Exposure to Study Treatments

In Table 6, data for exposure to placebo and tafamidis 80 mg are provided. The mean (standard deviation [SD]) duration of exposure was 22.0 (9.7) months for placebo and 23.8 (9.6) months for tafamidis 80 mg. Adherence to treatment was defined as number of days dosed divided by the number of days participating in the study. Patients were considered to be adherent to dosing if they took four capsules of study medication per day on at least 80% of the days of study participation (patients with less than 80% adherence were excluded from the per-protocol analysis set). Adherence was 80% or greater for 97% of patients in the placebo and 98.2% in the tafamidis 80 mg groups. A dose reduction was required in four patients on placebo and two patients on tafamidis 80 mg. A temporary discontinuation of dose was required in 46 patients (26%) on placebo and 33 patients (18.8%) on tafamidis 80 mg.

Medications that were taken after the first dose of the study drug were documented as concomitant medications. Table 7 shows concomitant cardiac drug treatments for the placebo, tafamidis 80 mg, and pooled tafamidis groups. A large percentage of patients were taking drugs that act on the renin-angiotensin system (27% versus 25% and 26%). Although calcium channel blockers were a prohibited medication, they were used by about 6% of patients assigned to placebo, 8% of patients assigned to tafamidis 80 mg, and 9% of patients in the pooled tafamidis group. There were a total of 56 instances of prohibited medication use (e.g., calcium channel blockers, digitalis, diflunisal) by 48 patients. These cases were reviewed by the clinical study team, which determined that no SAEs resulted

from the use of prohibited medications and these patients were included in all efficacy and safety analyses. Amiodarone or metoprolol were taken by close to one-third of patients. The majority of patients were on furosemide (78% versus 77% and 78%) and close to half were on spironolactone (46% versus 44% and 45%). Other commonly used cardiac treatments were antithrombotic (e.g., ASA, coumarin, apixaban, rivaroxaban, or heparin) and lipid-modifying drugs (e.g., atorvastatin or simvastatin).

Table 6: Exposure to Study Treatments (ITT Set)

	ATTR-ACT	
	Placebo (N = 177)	Tafamidis 80 mg (N = 176)
Duration, mean (SD), months	22.0 (9.7)	23.8 (9.6)
Adherence (%)[a]		
N	168	167
< 80%, n (%)	5 (3.0)	3 (1.8)
≥ 80%, n (%)	163 (97.0)	164 (98.2)
Dose reduction required due to AE, n (%)	4 (2.3)	2 (1.1)
Temporary discontinuation required due to AE, n (%)	46 (26.0)	33 (18.8)

AE = adverse event; ITT = intention to treat; SD = standard deviation.

[a] Number of days dosed divided by number of days participating in the study.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 7: Selected Concomitant Cardiac Drug Treatments (ITT Set)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg N = 176	Pooled tafamidis N = 264
Drugs acting on the renin-angiotensin system, n (%)	48 (27.1)	44 (25.0)	69 (26.1)
Calcium channel blockers, n (%)	11 (6.2)	14 (8.0)	23 (8.7)
Digoxin, n (%)	3 (1.7)	5 (2.8)	7 (2.7)
Amiodarone, n (%)	54 (30.5)	55 (31.3)	71 (26.9)
Selected beta-blockers, n (%)			
Atenolol	4 (2.3)	4 (2.3)	5 (1.9)
Bisoprolol	24 (13.6)	22 (12.5)	33 (12.5)
Carvedilol	26 (14.7)	15 (8.5)	35 (13.3)
Metoprolol	58 (32.8)	59 (33.5)	83 (31.4)
Selected diuretics, n (%)			
Furosemide	138 (78.0)	135 (76.7)	206 (78.0)
Bumetanide	26 (14.7)	27 (15.3)	41 (15.5)
Torasemide	69 (39.0)	65 (36.9)	99 (37.5)
Hydrochlorothiazide	20 (11.3)	15 (8.5)	29 (11.0)
Metolazone	46 (26.0)	27 (15.3)	45 (17.0)
Spironolactone	81 (45.8)	77 (43.8)	118 (44.7)
Eplerenone	27 (15.3)	23 (13.1)	39 (14.8)
Selected antithrombotic drug, n (%)			
ASA	73 (41.2)	64 (36.4)	98 (37.1)
Clopidogrel	12 (6.8)	14 (8.0)	18 (6.8)
Prasugrel	0 (0)	0 (0)	1 (0.4)
Ticagrelor	1 (0.6)	2 (1.1)	3 (1.1)
Acenocoumarol, coumarin, phenprocoumon, warfarin, or fluindione	77 (43.5)	80 (45.5)	129 (48.9)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg N = 176	Pooled tafamidis N = 264
Apixaban	37 (20.9)	35 (19.9)	57 (21.6)
Dabigatran	14 (7.9)	16 (9.1)	19 (7.2)
Edoxaban	1 (0.6)	2 (1.1)	2 (0.8)
Rivaroxaban	34 (19.2)	27 (15.3)	42 (15.9)
Heparin/LMWH[a]/heparinoid	59 (33.3)	57 (32.4)	78 (29.5)
Selected lipid-modifying drugs, n (%)			
Atorvastatin	43 (24.3)	41 (23.3)	66 (25.0)
Lovastatin	6 (3.4)	3 (1.7)	3 (1.1)
Pravastatin	11 (6.2)	15 (8.5)	19 (7.2)
Rosuvastatin	7 (4.0)	15 (8.5)	19 (7.2)
Simvastatin	39 (22.0)	32 (18.2)	40 (15.2)
Ezetimibe	7 (4.0)	4 (2.3)	5 (1.9)

ASA = acetylsalicylic acid; ITT = intention to treat; LMWH = low-molecular-weight heparin.

[a] Includes bemiparin, dalteparin, enoxaparin, nadroparin, and tinzaparin.

Source: Clinical Study Report for ATTR-ACT.[7]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported. See Appendix 3 for detailed efficacy data of the outcomes in the review protocol.

Overall Survival, All-Cause and Cardiovascular Mortality and Hospitalization

Table 8 shows the primary outcomes of all-cause mortality and cardiovascular-related hospitalization. At month 30, more patients were alive in the tafamidis 80 mg group compared with placebo (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with tafamidis 80 mg among patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). In the primary analysis that compared the pooled tafamidis dose group with placebo, the results demonstrated a pattern that was similar to tafamidis 80 mg. The Finkelstein-Schoenfeld analysis was statistically significant for the pooled tafamidis group versus placebo (P = 0.0006), demonstrating that at least one, or possibly both, outcomes (all-cause mortality and cardiovascular-related hospitalization) were statistically significantly different.

Table 8: All-Cause Mortality and Cardiovascular-Related Hospitalization (ITT Set)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg[a] N = 176	Pooled tafamidis N = 264
All-cause mortality			
Alive, n (%)	101 (57.1)	122 (69.3)	186 (70.5)
CV-related hospitalization			
Mean per patient per year[b]	0.46	0.34	0.30
Finkelstein-Schoenfeld P value	Reference	0.0030	0.0006

CV = cardiovascular; ITT = intention to treat.

[a] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[b] Among patients alive at month 30. Number of CV-related hospitalizations per year is calculated as patient's number of CV-related hospitalizations divided by years on study.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 21 in Appendix 3 shows the primary outcomes for the tafamidis 80 mg and pooled tafamidis groups versus placebo for the per-protocol set. The results were consistent with the ITT analysis set, with a between-groups difference favouring tafamidis (P = 0.0002 for tafamidis 80 mg and P < 0.0001 for pooled tafamidis). Sensitivity analyses are presented in Table 22, Table 23, and Table 24 in Appendix 3. With multiple imputation of missing cases (Table 22), more patients were alive in the tafamidis pooled group compared with placebo; however, cardiovascular-related hospitalizations per patient per year were higher in the pooled tafamidis group compared with the placebo group. The overall test was statistically significant (P = 0.0008). Similar results were observed for a sensitivity analysis that excluded hospitalizations adjudicated as indeterminate (P = 0.0006) (Table 23) and a sensitivity analysis that did not classify transplantation or CMAD implantation as death (P = 0.0003) (Table 24).

Exploratory subgroup analyses for the pooled tafamidis group versus placebo by TTR genotype (wild-type or hereditary) and NYHA baseline classification (class I/II combined or class III) are presented in Table 25, Appendix 3. Subgroup analyses were not available for tafamidis 80 mg. For patients with wATTR-CM, more patients in the tafamidis pooled group were alive at month 30 and, among those who were alive, there were fewer cardiovascular-related hospitalizations compared with placebo. For patients with hATTR-CM, more patients in the tafamidis pooled group were alive at month 30 compared with placebo. It was also observed that the number of cardiovascular-related hospitalizations among patients who were alive was higher for the tafamidis pooled group versus placebo based on an exploratory subgroup analysis. In patients with an NYHA classification of I or II at baseline, more patients who received tafamidis were alive at month 30 and the rate of cardiovascular-related hospitalization was lower compared with placebo. In patients with an NYHA classification of III at baseline, slightly more patients were alive at month 30; however, the rate of cardiovascular-related hospitalization was higher compared with placebo.

Table 9 presents separate data for all-cause, cardiovascular-related, and indeterminate causes of death and hospitalization. These were all exploratory analyses. Death (excluding patients with transplants or CMADs) occurred in 40.7% of patients in the placebo group, 27.8% of patients in the tafamidis 80 mg group, and 27.3% in the pooled tafamidis group. Cardiovascular causes of death occurred in 28% of patients in the placebo group, 20.5% of patients in the tafamidis 80 mg group, and 20% of patients in the pooled tafamidis group. Non-cardiovascular causes of death were 7% of patients in the placebo group, 5% of patients in the tafamidis 80 mg group, and 5% of patients in the tafamidis pooled group. Nine deaths

(5.1%) in the placebo group were indeterminate, as were four deaths (2.3%) in the tafamidis 80 mg group, and five deaths (1.9%) in the pooled tafamidis group. Hospitalizations for any cause were present in 77% of patients in the placebo group, 71% of patients in the tafamidis 80 mg group, and 72% of patients in the pooled tafamidis group. Most hospitalizations were cardiovascular-related (60.5% versus 54.5% and 52%). The causes of three hospitalizations in the tafamidis group were indeterminate. The rate ratio for all-cause hospitalization for the pooled tafamidis group versus placebo was 0.79 (95% CI, 0.69 to 0.91). The rate ratio for cardiovascular-related hospitalization was 0.68 (95% CI, 0.56 to 0.81).

Table 9: Detailed Mortality and Hospitalization (ITT Set)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg[a] N = 176	Pooled tafamidis N = 264
Mortality (month 30)			
Total deaths, n (%)[a]	72 (40.7)	49 (27.8)	72 (27.3)
CV-related	50 (28.2)	36 (20.5)	53 (20.1)
Non–CV related	13 (7.3)	9 (5.1)	14 (5.3)
Indeterminate	9 (5.1)	4 (2.3)	5 (1.9)
Hospitalization (month 30)			
Total hospitalized, n (%)[b]	136 (76.8)	125 (71.0)	190 (72.0)
CV-related	107 (60.5)	96 (54.5)	138 (52.3)
Non–CV related	80 (45.2)	81 (46.0)	125 (47.3)
Indeterminate	0 (0)	2 (1.1)	3 (1.1)
Number of all-cause hospitalizations per patient per year (95% CI)[c]	1.16 (1.05 to 1.29)	NR	0.92 (0.84 to 1.01)
All-cause hospitalization rate ratio (95% CI)[d]	Reference	NR	0.79 (0.69 to 0.91)
P value	Reference	NR	0.0007
Number of CV hospitalization per patient per year (95% CI)[b]	0.70 (0.62 to 0.80)	NR	0.48 (0.42 to 0.54)
CV hospitalization rate ratio (95% CI)	Reference	NR	0.68 (0.56 to 0.81)
P value	Reference	NR	< 0.0001
All-cause hospitalization: days hospitalized, mean (SD)[b]	18.45 (24.33)	NR	15.51 (24.32)
LS mean difference (95% CI)[d]	Reference	NR	−2.70 (−7.3 to 1.9)
P value	Reference	NR	0.2480
CV days hospitalized, mean (SD)[b]	12.10 (20.84)	NR	8.30 (15.02)
LS mean difference (95% CI)[d]	Reference	NR	−3.72 (−7.1 to −0.4)
P value	Reference	NR	0.0287

CI = confidence interval; CV = cardiovascular; ITT = intention to treat; LS = least squares; NR = not reported; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin.

[a] The number of deaths reported in this table was the number of deaths that occurred during the study period and the follow-up period (those who died following premature withdrawal from the study). Deaths reported here were considered exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method. Deaths (recorded on the notice of death case report form) that occurred up to 30 months post-randomization are counted.

[b] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

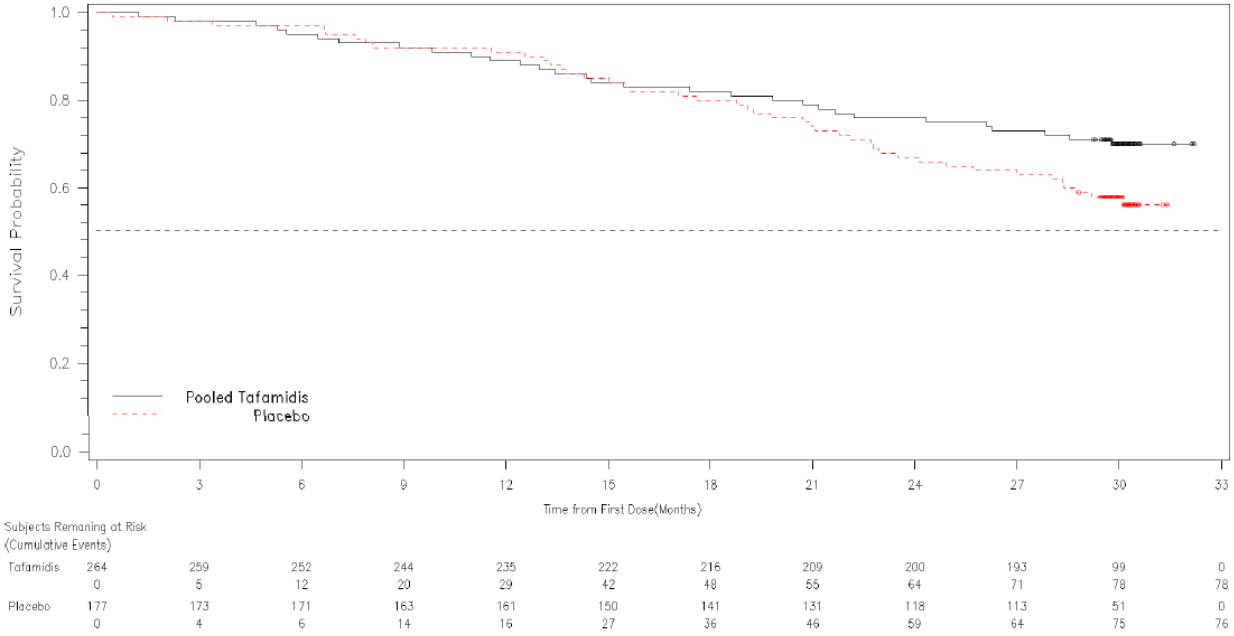
[c] Frequency of hospitalizations over the duration of the trial, which was defined as the number of times a patient was hospitalized (i.e., admitted to a hospital).

[d] From a Poisson regression, with treatment, TTR genotype (wild-type or hereditary), NYHA baseline classification (class I and II combined and class III), treatment by TTR genotype interaction, treatment by NYHA baseline classification interaction, and treatment duration.

Source: Clinical Study Report for ATTR-ACT.[7]

The survival curve over 30 months for the pooled tafamidis versus placebo groups is shown in Figure 3. An effect on overall survival began after about 18 months of treatment. The HR for overall survival from a Cox proportional hazards model with TTR genotype (wild-type or hereditary) and NYHA baseline classification (class I/II or class III) as factors was 0.69 (95% CI, 0.49 to 0.98), for tafamidis 80 mg versus placebo (Table 10). The HR (95% CI) was 0.70 (0.51 to 0.96) for the pooled tafamidis group versus placebo. For cardiovascular-related mortality, the HRs (95% CI) for tafamidis 80 mg versus placebo and pooled tafamidis versus placebo were 0.69 (0.47 to 1.01) and 0.69 (0.49 to 0.98), respectively.

Figure 3: Time to All-Cause Mortality (ITT Set)



ITT = intention to treat.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 10: Time to All-Cause Mortality and Cardiovascular-Related Mortality (ITT Set)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg N = 176	Tafamidis pooled N = 264
All-cause mortality (month 30)[a]			
Total deaths, n (%)	76 (42.9)	54 (30.7)	78 (29.5)
HR (95% CI)[b]	Reference	0.69 (0.49 to 0.98)	0.70 (0.51 to 0.96)
P value	Reference	0.0378	0.0259
CV-related mortality (month 30)[a]			
Total events, n (%)	63 (35.6)	45 (25.6)	64 (24.2)
CV deaths,[c] n (%)	59 (33.3)	37 (21.0)	55 (20.8)
Heart transplant,[d] n (%)	4 (2.3)	6 (3.4)	7 (2.7)
CMAD implantation, n (%)	0 (0)	2 (1.1)	2 (0.8)
HR (95% CI)[b]	Reference	0.69 (0.47 to 1.01)	0.69 (0.49 to 0.98)
P value	Reference	0.0579	0.0383

CI = confidence interval; CMAD = cardiac mechanical assist device; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; NYHA = New York Heart Association; TTR = transthyretin.

[a] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[b] From a Cox proportional hazards model with TTR genotype (wild-type and variant) and NYHA baseline classification (class I and II combined and class III) in the model.

[c] Includes deaths that were CV-related and indeterminate.

[d] Includes heart and heart-combination transplants.

Source: Clinical Study Report for ATTR-ACT.[7]

HRQoL

Table 11 and Figure 4 present data for the key secondary outcome of KCCQ overall score. The KCCQ was tested only if the primary outcomes and 6MWT results were statistically significant. The change from baseline to month 30 was −7.3 points in the tafamidis 80 mg group, −7.2 points for the pooled tafamidis group, and −20.8 points for the placebo group, indicating a relatively more rapid decline in patients' HRQoL as measured by KCCQ over the 30-month period. The least squares mean difference in change from baseline for the pooled tafamidis group versus placebo was 13.7 points (95% CI, 9.5 to 17.8). Figure 4 shows the KCCQ overall score over time, where a benefit with tafamidis in HRQoL was observed as early as month 6. Table 26 in Appendix 3 presents the pattern mixture analysis for patients with KCCQ data at month 30 and results were consistent with the main analysis.

Table 11: Kansas City Cardiomyopathy Questionnaire (Overall Score) (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	177[b]	65.9 (21.7)	53.8 (24.4)	−20.8 (2.0)	84	Reference	Reference
Tafamidis 80 mg[c]	176[b]	67.1 (21.3)	68.8 (21.4)	−7.3 (1.5)	[redacted]	[redacted]	[redacted]
Pooled tafamidis	264[b]	67.3 (21.4)	68.2 (21.9)	−7.2 (1.4)	170	13.7 (9.5 to 17.8)	< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention to treat; LS = least squares; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error; TTR = transthyretin.

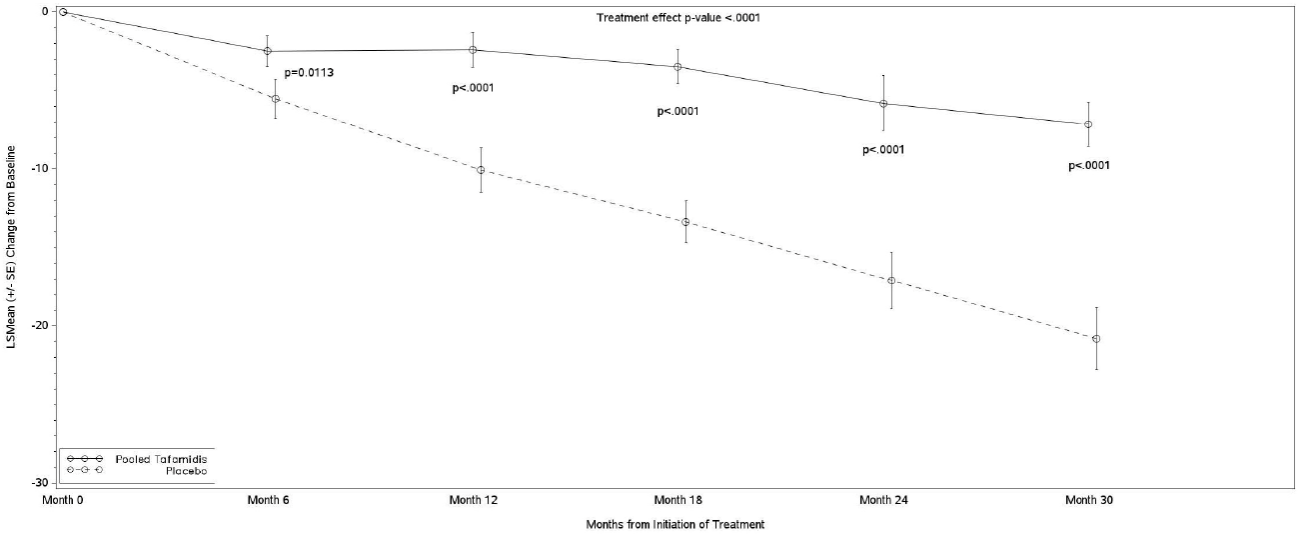
[a] LS mean is from an MMRM ANCOVA model with random effects of the study centre and patient; fixed effects of treatment, visit, TTR genotype (wild-type and variant), and visit by treatment interaction; and covariate of baseline score.

[b] At month 30, N equals 84 for placebo, 170 for tafamidis pooled, and 110 for tafamidis 80 mg.

[c] Exploratory analysis.

Source: Clinical Study Report for ATTR-ACT.[7]

Figure 4: KCCQ (Overall Score) by Time (ITT Set)



ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; SE = standard error.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 27 in Appendix 3 presents the KCCQ scores by domain. The change from baseline to month 30 was smaller in the negative direction for tafamidis 80 mg and the pooled tafamidis group compared with placebo on the domains of physical limitation, symptom frequency, symptom burden, total symptoms, quality of life, social limitation, and clinical summary.

Table 28 in Appendix 3 presents KCCQ overall score for subgroups of wild-type, hereditary, NYHA baseline class I/II, and NYHA baseline class III for tafamidis pooled versus placebo. For all subgroups, the change from baseline to month 30 in the pooled tafamidis group was smaller in the negative direction.

The least squares mean change from baseline to month 30 on the EQ-5D-3L index score was −0.05 for the pooled tafamidis group and −0.14 for placebo (least squares mean difference = 0.09; 95% CI, 0.05 to 0.12) (Table 12). For the EQ VAS, the least squares mean change from baseline was also in favour of the pooled tafamidis group over placebo.

Table 12: Generic HRQoL (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
EQ-5D-3L index score[b]							
Placebo	177[c]	0.80 (0.15)	0.72 (0.22)	−0.14 (0.02)	84	Reference	Reference
Pooled tafamidis	264[c]	0.80 (0.16)	0.80 (0.17)	−0.05 (0.01)	169	0.09 (0.05 to 0.12)	< 0.0001
EQ VAS[b]							
Placebo	177[c]	66.5 (17.8)	58.0 (21.4)	−12.9 (1.6)	84	Reference	Reference
Pooled tafamidis	264[c]	68.3 (18.6)	68.0 (19.1)	−3.8 (1.2)	166	9.1 (5.4 to 12.8)	< 0.0001

ANCOVA = analysis of covariance: CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; EQ VAS = EuroQol Visual Analogue Scale; ITT = intention to treat; LS = least squares; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error.

[a] LS mean is from an MMRM ANCOVA model with random effects of the study centre and patient; fixed effects of treatment, visit, and TTR genotype (wild-type or variant) and visit by treatment interaction; and covariate of baseline score.

[b] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[c] At month 30, N equals 84 for placebo and 169 for tafamidis pooled.

Source: Clinical Study Report for ATTR-ACT.[7]

For the PGA, slightly more patients in the pooled tafamidis group reported improvements (very much improved = 3.0% versus 2.6%; much improved = 15.3% versus 12.3%; and minimally improved = 20.8% versus 20.1%) from baseline to month 30 compared with placebo. A similar percentage of patients in both groups reported no change from baseline (45.8% versus 46.1%). More patients in the placebo group reported worsening (minimally worse = 12.7% versus 14.9%; much worse = 3.4% versus 5.2%; and very much worse = 0.4% versus 1.9%).

NYHA Classification

Changes in NYHA classification from baseline are shown in Table 13. Worsening from class I to class II or class III occurred in about 3% of patients on placebo and 4.5% of patients on tafamidis. Worsening from class II to class III or class IV occurred in about 15% of patients on placebo and 13% of patients on tafamidis. Worsening from class III to class IV occurred in two patients in each group. More patients on tafamidis improved from class II to class I (5.3% versus 1.7%) or from class III to class II (3.4% versus 2.8%). No change was reported by 23.2% of patients in the placebo and 37.5% in the pooled tafamidis pooled groups.

Table 13: NYHA Classification (ITT Set)

NYHA class change from baseline[a]	ATTR-ACT	
	Placebo N = 177[b]	Pooled tafamidis N = 264[b]
No change from baseline to month 30, n (%)	41 (23.2)	99 (37.5)
Class I	1 (0.6)	7 (2.7)
Class II	28 (15.8)	73 (27.7)
Class III	12 (6.8)	19 (7.2)
Class IV	0 (0)	0 (0)
Worsened from class I, n (%)	5 (2.8)	12 (4.5)
Class I to class II	4 (2.3)	7 (2.7)
Class I to class III	1 (0.6)	4 (1.5)
Class I to class IV	0 (0)	1 (0.4)
Worsened from class II, n (%)	26 (14.7)	35 (13.3)
Class II to class III	22 (12.4)	35 (13.3)
Class II to class IV	4 (2.3)	0 (0)
Worsened from class III, n (%)	2 (1.1)	2 (0.8)
Improved from class II, n (%)	3 (1.7)	14 (5.3)
Improved from class III, n (%)	5 (2.8)	9 (3.4)
Class III to class II	5 (2.8)	9 (3.4)
Class III to class I	0 (0)	0 (0)
Improved from class IV, n (%)[c]	0 (0)	0 (0)

ITT = intention to treat; NYHA = New York Heart Association.

[a] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[b] At month 30, N equals 82 for placebo and 171 for tafamidis pooled.

[c] No patient was NYHA class IV at baseline.

Source: Clinical Study Report for ATTR-ACT.[7]

Disability

The key secondary outcome of 6MWT is shown in Table 14 and Figure 5. Statistical testing of the 6MWT was undertaken only if the primary outcome was statistically significant. The decrease in the 6MWT from baseline to month 30 was smaller for tafamidis 80 mg compared with placebo (least squares mean change = −54.8 metres versus −130.6 metres). Similarly, for the pooled tafamidis group, the decrease was smaller compared with placebo (−54.9 metres). The least squares mean difference for the pooled tafamidis group versus placebo was 75.7 metres (95% CI, 57.6 to 93.8). Figure 5 shows the 6MWT over time; a difference between the pooled tafamidis group and placebo was observed at month 6. Table 29 in Appendix 3 presents the pattern mixture analysis for patients with 6MWT data at month 30; results were consistent with the main analysis.

Table 30 in Appendix 3 presents the 6MWT for subgroups. In all subgroups, the decrease in the distance walked from baseline to month 30 was smaller for the pooled tafamidis group compared with placebo. However, for patients with NYHA baseline class III, the magnitude of the difference between placebo and tafamidis was smaller than the other subgroups.

Table 14: Six-Minute Walk Test (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD) (metres)	Mean (SD) (metres)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	177[b]	353.3 (126.0)	333.8 (117.5)	−130.6 (9.8)	70	Reference	Reference
Tafamidis 80 mg[c]	176[b]	344.8 (120.3)	364.7 (126.1)	−54.8 (7.5)	[redacted]	[redacted]	[redacted]
Pooled tafamidis	264[b]	350.6 (121.3)	370.4 (119.4)	−54.9 (5.1)	155	75.7 (57.6 to 93.8)	< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention to treat; LS = least squares; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error; TTR = transthyretin.

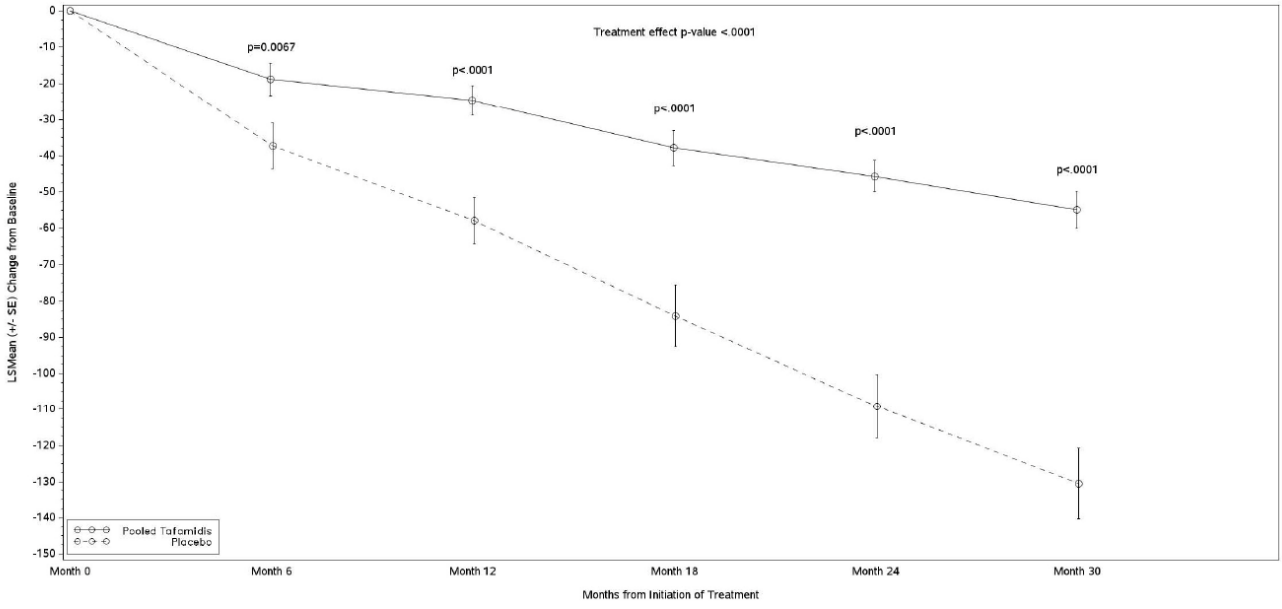
[a] LS mean is from an MMRM ANCOVA model with random effects of the study centre and patient; fixed effects of treatment, visit, TTR genotype (wild-type or variant), and visit by treatment interaction; and covariate of baseline score.

[b] At month 30, N equals 70 for placebo, 155 for tafamidis pooled, and 101 for tafamidis 80 mg.

[c] Exploratory analysis.

Source: Clinical Study Report for ATTR-ACT.[7]

Figure 5: Six-Minute Walk Test by Time (ITT Set)



ITT = intention to treat; SE = standard error.

Source: Clinical Study Report for ATTR-ACT.[7]

Cardiac Biomarkers

Table 15 presents data for the NT-proBNP cardiac biomarker, which was an exploratory outcome. In both groups, NT-proBNP increased from baseline to month 30; however, the increase was smaller for the pooled tafamidis group compared with placebo (least squares mean change from baseline, 1,771.7 pg/mL versus 3,947.7 pg/mL, respectively).

Table 15: N-Terminal Prohormone of Brain Natriuretic Peptide (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD) (pg/mL)[a]	Mean (SD) (pg/mL)[a]	LS mean[b] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention to treat; LS = least squares; SD = standard deviation; SE = standard error.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Echocardiogram Parameters

Changes from baseline to month 30 in echocardiogram parameters are presented in Table 16. Smaller magnitudes of changes were observed for GLS, LV end diastolic interventricular septal wall thickness, LV posterior wall thickness, and LVEF for the pooled tafamidis group compared with placebo.

Table 16: Echocardiogram Parameters

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
GLS (%)[b]							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LV end diastolic interventricular septal wall thickness (mm)[b]							
Placebo[c]	[redacted]	16.2 (3.5)	16.2 (2.9)	0.33 (0.34)	[redacted]	Reference	[redacted]
Pooled tafamidis[c]	[redacted]	16.7 (3.8)	16.1 (3.0)	−0.11 (0.24)	[redacted]	−0.44 (−1.1 to 0.23)	[redacted]
LV posterior wall thickness (mm)[b]							
Placebo	[redacted]	16.7 (4.1)	17.4 (3.4)	1.2 (0.4)	[redacted]	Reference	[redacted]
Pooled tafamidis	[redacted]	17.0 (3.9)	17.4 (3.5)	0.9 (0.4)	[redacted]	−0.3 (−1.6 to 1.0)	[redacted]
LVEF (%)[b]							
Placebo	[redacted]	48.6 (9.5)	46.0 (9.3)	−4.3 (1.1)	[redacted]	Reference	[redacted]
Pooled tafamidis	[redacted]	48.4 (10.3)	47.8 (9.4)	−2.8 (0.9)	[redacted]	1.5 (−0.6 to 3.6)	[redacted]

CI = confidence interval; GLS = global longitudinal strain; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; SD = standard deviation; SE = standard error.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Nutritional Status

The mBMI decreased from baseline to month 30 for both the pooled tafamidis group and placebo; however, the change was smaller for patients who received tafamidis (least squares mean change from baseline = −31.7 kg/m^2*g/L versus −54.5 kg/m^2*g/L).

Table 17: Modified Body Mass Index (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control[a]		
		Mean (SD) (kg/m^2*g/L)	Mean (SD) (kg/m^2*g/L)	LS mean[b] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	177[c]	1,066.4 (194.4)	1,042.5 (171.4)	−54.5 (6.2)	82	Reference	Reference
Pooled tafamidis	264[c]	1,058.8 (173.8)	1,045.3 (172.5)	−31.7 (5.9)	171	22.8 (5.5 to 40.2)	0.010

ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; ITT = intention to treat; LS = least squares; mBMI = modified body mass index; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error; TTR = transthyretin.

[a] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[b] LS mean was from an MMRM ANCOVA model with random effects of the study centre and patient; fixed effects of treatment, visit, TTR genotype (wild-type or variant), and visit by treatment interaction; and covariate of baseline score (exploratory outcome).

[c] At month 30, N equals 82 for placebo and 171 for tafamidis pooled.

Source: Clinical Study Report for ATTR-ACT.[7]

Need for Heart or Liver Transplant or Cardiac Device Implantation

Heart or combined heart/liver transplants were received by four patients in the placebo group, six patients in the tafamidis 80 mg group, and seven patients in the pooled tafamidis group (Table 18). CMAD implantation occurred in two patients who received tafamidis 80 mg.

Table 18: Transplant and Implantation of CMAD (ITT Set)

	ATTR-ACT		
	Placebo N = 177	Tafamidis 80 mg[a] N = 176	Tafamidis pooled N = 264
Transplant/CMAD (month 30)			
Heart transplant, n (%)[a,b]	4 (2.3)	6 (3.4)	7 (2.7)
CMAD implantation, n (%)[a]	0 (0)	2 (1.1)	2 (0.8)

CMAD = cardiac mechanical assist device; ITT = intention to treat.

[a] Exploratory and not part of the statistical hierarchy testing of the Finkelstein-Schoenfeld method.

[b] Includes heart and heart-combination transplants.

Source: Clinical Study Report for ATTR-ACT.[7]

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 19 for detailed harms data.

AEs

Most patients experienced at least one AE (98.9% placebo, 98.3% tafamidis 80 mg, and 98.5% pooled tafamidis). Among the most common events were cardiac-related (i.e., atrial fibrillation: 18.6% placebo, 19.9% tafamidis 80 mg, and 19.3% pooled tafamidis; and cardiac failure: 33.9% placebo, 26.1% tafamidis 80 mg, and 28.8% pooled tafamidis). Gastrointestinal effects, such as constipation (16.9% placebo, 14.8% tafamidis 80 mg, and 15.2% pooled tafamidis), diarrhea (22.0% placebo, 12.5% tafamidis 80 mg, and 12.1% pooled tafamidis), and nausea (20.3% placebo, 11.4% tafamidis 80 mg, and 11.0% pooled tafamidis) were also common but experienced by a lower percentage of patients who received tafamidis compared with those who received placebo. Urinary tract infection was experienced by more patients in the placebo group than in the tafamidis 80 mg group and the pooled tafamidis group (15.3% versus 9.1% and 9.5%, respectively). Other common AEs are listed in Table 19 and generally occurred more frequently in the placebo group. More patients in the tafamidis 80 mg group than in the placebo group experienced cataract (5.1% versus 1.1%), asthenia (10.2% versus 6.2%), balance disorder (8.5% versus 1.1%), cystitis (3.4% versus 0%), and sinusitis (5.7% versus 0.6%).

SAEs

At least one SAE was experienced by 79.1% of patients in the placebo group, 75.6% of patients in the tafamidis 80 mg group, and 75.4% of patients in the pooled tafamidis group. The most common SAEs were cardiac-related (i.e., atrial fibrillation and cardiac failure) and condition-aggravated (32.8% placebo, 22.7% tafamidis 80 mg, and 23.1% pooled tafamidis). Falls were slightly more frequent in the tafamidis group (2.8% placebo, 5.1% tafamidis 80 mg, and 5.3% pooled tafamidis).

Withdrawals Due to Adverse Events

More patients in the placebo group stopped treatment due to AEs than in the tafamidis 80 mg and pooled tafamidis groups (28.8% versus 22.7% and 21.2%, respectively). The number of withdrawals from the study was similar for the placebo, tafamidis 80 mg, and tafamidis pooled groups (6.2% versus 6.8% and 6.4%, respectively). The most common AEs leading to withdrawal were not summarized.

Notable Harms

Hypothyroidism was experienced by 5.6% of patients in the placebo group, 6.8% of patients in the tafamidis 80 mg group, and 6.4% of patients in the pooled tafamidis group. More patients who received tafamidis had a thyroxine abnormality of less than 0.8 of the lower limit of normal (4.5% placebo, 29.9% tafamidis 80 mg, and 23.9% pooled tafamidis). Pruritis or rash occurred in more patients in the placebo group.

Table 19: Summary of Harms (Safety Set)

	ATTR-ACT		
	Placebo (N = 177)	Tafamidis 80 mg (N = 176)	Pooled tafamidis (N = 264)
Patients with ≥ 1 adverse event			
n (%)	175 (98.9)	173 (98.3)	260 (98.5)
Most common events, n (%)[a]			
Atrial fibrillation	33 (18.6)	35 (19.9)	51 (19.3)
Cardiac failure	60 (33.9)	46 (26.1)	76 (28.8)
Congestive cardiac failure	33 (18.6)	22 (12.5)	39 (14.8)

	ATTR-ACT		
	Placebo (N = 177)	Tafamidis 80 mg (N = 176)	Pooled tafamidis (N = 264)
Constipation	30 (16.9)	26 (14.8)	40 (15.2)
Diarrhea	39 (22.0)	22 (12.5)	32 (12.1)
Nausea	36 (20.3)	20 (11.4)	29 (11.0)
Fatigue	33 (18.6)	29 (16.5)	45 (17.0)
Peripheral edema	31 (17.5)	30 (17.0)	47 (17.8)
Urinary tract infection	27 (15.3)	16 (9.1)	25 (9.5)
Fall	41 (23.2)	43 (24.4)	70 (26.5)
Fluid overload	29 (16.4)	19 (10.8)	32 (12.1)
Gout	29 (16.4)	18 (10.2)	28 (10.6)
Pain in extremity	20 (11.3)	27 (15.3)	33 (12.5)
Dizziness	37 (20.9)	25 (14.2)	42 (15.9)
Acute kidney injury	29 (16.4)	17 (9.7)	29 (11.0)
Cough	30 (16.9)	21 (11.9)	37 (14.0)
Dyspnea	55 (31.1)	29 (16.5)	50 (18.9)
Pleural effusion	32 (18.1)	14 (8.0)	26 (9.8)
Patients with ≥ 1 SAE			
n (%)	140 (79.1)	133 (75.6)	199 (75.4)
Most common events, n (%)[b]			
Atrial fibrillation	8 (4.5)	11 (6.3)	18 (6.8)
Cardiac failure	40 (22.6)	34 (19.3)	50 (18.9)
Acute cardiac failure	17 (9.6)	23 (13.1)	27 (10.2)
Congestive cardiac failure	31 (17.5)	21 (11.9)	35 (13.3)
Condition-aggravated	58 (32.8)	40 (22.7)	61 (23.1)
Disease progression	12 (6.8)	13 (7.4)	18 (6.8)
Pneumonia	12 (6.8)	13 (7.4)	19 (7.2)
Fall	5 (2.8)	9 (5.1)	14 (5.3)
Syncope	10 (5.6)	6 (3.4)	6 (2.3)
Acute kidney injury	15 (8.5)	13 (7.4)	22 (8.3)
Pleural effusion	4 (2.3)	6 (3.4)	11 (4.2)
Patients who stopped treatment due to adverse events			
n (%)	51 (28.8)	40 (22.7)	56 (21.2)
Patients who discontinued from the study due to adverse events			
n (%)	11 (6.2)	12 (6.8)	17 (6.4)
Deaths			
n (%)	72 (40.7)	49 (27.8)	72 (27.3)
Underlying disease	49 (27.7)	28 (15.9)	45 (17.0)
Other cause	20 (11.3)	17 (9.7)	22 (8.3)
Unknown cause	3 (1.7)	4 (2.3)	5 (1.9)
Notable harms			
Hypothyroidism, n (%)	10 (5.6)	12 (6.8)	17 (6.4)
Thyroxine abnormality < 0.8 LLN, n/N (%)	7/157 (4.5)	47/157 (29.9)	57/238 (23.9)
Pruritis, n (%)	15 (8.5)	12 (6.8)	16 (6.1)
Rash, n (%)	12 (6.8)	6 (3.4)	9 (3.4)

LLN = lower limit of normal; SAE = serious adverse event.

[a] Frequency ≥ 15%.

[b] Frequency ≥ 5%.

Source: Clinical Study Report for ATTR-ACT.[7]

Critical Appraisal

Internal Validity

Patients were randomized with an interactive web-response system and stratified by TTR genotype (wild-type or hereditary) and baseline NYHA classification (class I and class II/III combined). There were slight imbalances in baseline NT-proBNP level and NYHA class III, where patients randomized to placebo had higher NT-proBNP and more patients were in class III. This suggests that some patients in the placebo group may have had more severe cardiomyopathy. However, these slight differences in NT-proBNP and NYHA class III would likely not have a major impact on the difference in the mortality results between tafamidis and placebo. Blinding was maintained by administering four capsules daily to all patients, which consisted of either three capsules of matching placebo plus one capsule of tafamidis 20 mg, four capsules of tafamidis 20 mg, or four capsules of placebo. Initially, the active treatment and placebo capsules had a different appearance, which was communicated as a concern by the FDA in 2013. Subsequently, the placebo and active treatment capsules were provided with the same appearance to prevent compromises in blinding. Patients received the original placebo formulation for about three months and, during this time, no patient who received the original placebo formulation discontinued the study.

A statistical hierarchy testing procedure was employed that appropriately maintained the type I error rate at 0.05 for the primary and key secondary outcomes. The primary analysis for all-cause mortality and cardiovascular-related hospitalization was done using the Finkelstein-Schoenfeld method. This method compares each patient with every other patient in a pairwise manner within each stratum (wild-type and hereditary, and NYHA class I/II combined and NYHA class III) on all-cause mortality, and then on cardiovascular-related hospitalization if patients did not differ on mortality. Higher priority is given to the outcome of most clinical importance which, in this case, is all-cause mortality. This method overcomes a limitation associated with composite outcomes due to assigning equal value to all components.[33]

The 30-month study was completed by 48% of patients in the placebo group, 64% in the tafamidis 80 mg group, and 65.5% in the tafamidis pooled group. More patients in the placebo group discontinued from treatment (52% in the placebo group versus 36% in the tafamidis 80 mg and 34.5% tafamidis pooled groups). The main reason for discontinuation was death, which was higher in the placebo group (21.5% versus 14% and 15%). Over the course of the study, a larger percentage of patients in the placebo group withdrew consent (21% versus about 10% for tafamidis), and whether this may have been due to knowledge of treatment assignment or worsening of disease condition is unclear. Several measures were taken to minimize the impact of early discontinuation on the assessment of outcomes. For example, each patient was asked to provide consent to allow their medical records to be accessed in the event they could not be contacted at month 30. If the patient or designated contact could not be reached, then the patient's primary physician was contacted, or appropriate national/regional registries were searched to ascertain vital status. Moreover, cardiovascular-related death or hospitalization was adjudicated by an independent adjudication committee. Those measures may have ensured the completeness in reporting mortality and the correct identification of the cause of death.

Nonetheless, due to the large number of patients who did not complete the trial, there was a considerable amount of missing data for the key secondary and exploratory outcomes. For example, for the KCCQ, the difference from baseline to month 30 between tafamidis

and placebo was based on only 47.5% of patients on placebo, 62.5% of patients on tafamidis 80 mg, and 64.4% of patients in the tafamidis pooled group. Similarly, for the 6MWT, the 30-month estimate was based on 39.5% of patients on placebo, 57.4% on tafamidis 80 mg, and 58.7% of patients in the tafamidis pooled group. No imputation of missing data was conducted, although a pattern mixture analysis was carried out for the KCCQ and 6MWT that included the pattern of missing data in the MMRM ANCOVA models, and which yielded results that were similar to the main analyses. In addition, if the higher number of withdrawals from the trial in the placebo group due to death had introduced bias, then the direction of bias is anticipated to have favoured placebo because patients who remained in the placebo group would be "healthier" than those who discontinued. However, the results for both the KCCQ and 6MWT were still in favour of tafamidis despite the direction of the potential bias. Similarly, low numbers of patients were included in the 30-month analyses of the exploratory outcomes of EQ-5D-3L, NT-proBNP, echocardiogram parameters, and mBMI. The exclusion of patients from these analyses due to death and withdrawal of consent does introduce uncertainty in the estimates and compromises the original randomization of patients into the trial.

Prohibited medications included calcium channel blockers, digitalis, diflunisal, and certain other NSAIDs. Calcium channel blockers and digitalis were prohibited because they bind to amyloid fibrils and may increase risk of toxicity. Diflunisal and other NSAIDs were prohibited because they bind to thyroxine binding sites on TTR and may interfere with the mechanism of action of tafamidis. However, many patients were found to be using prohibited medication (especially calcium channel blockers, which were used by about 6% of patients on placebo and 8% of patients on tafamidis 80 mg). The data for these patients were still incorporated into efficacy and safety analyses, as it was deemed that they did not present with any SAEs due to the use of the prohibited medications. Patients using prohibited medications were required to discontinue these medications after they were identified, but not required to discontinue from the study.

External Validity

The patients in the trial were elderly, with the majority being male and white. Patients with NYHA classes I to III were included, with less than 10% in class I, about 60% in class II, and about 30% in class III. About 75% of patients had wATTR-CM and 25% had hATTR-CM, with the most common mutation being V142I or V122I. The clinical experts consulted for this review indicated that the patient characteristics were representative of the patients they see in clinical practice, although a larger percentage (close to 90%) will have wATTR-CM. Also, concomitant medications used by patients, such as diuretics, were representative of practice in Canada. Subgroups with wild-type or hereditary forms, and patients in NYHA class I/II or class III, were examined. These subgroups are relevant to clinical practice, as wild-type and hereditary are the two major forms of ATTR-CM for which tafamidis is indicated and the NYHA classification system is the most common way to assess disease severity.

One inclusion criterion for entry into ATTR-ACT was an NT-proBNP concentration of 600 pg/mL or higher; the clinical experts consulted by CADTH for this review indicated that this was a reasonable level, as a normal concentration is 400 pg/mL or less. They also indicated that the exclusion criterion of an estimated glomerular filtration rate of less than 25 mL/min/1.73m^2 may not be applied in practice and was not a criterion for entry into the long-term extension study. Patients with NYHA class IV or previous heart/liver transplant were excluded and, therefore, the results cannot be applied to these patient populations. This should not pose a significant limitation. The clinical experts indicated that

patients with NYHA class IV are not anticipated to benefit from treatment with tafamidis and that only a small proportion of patients with ATTR-CM undergo heart transplantation in Canada.

Tafamidis was administered as a 20 mg or 80 mg dose once daily and the primary analysis was conducted on the pooled tafamidis group (i.e., a combination of the 20 mg and 80 mg doses). The dose of interest in the current review is 80 mg once daily based on the Health Canada–recommended dose. However, all analyses based on the 80 mg dose were exploratory and statistical conclusions for the 80 mg dose could not be made directly. The pooled group contained one-third of the patients taking tafamidis 20 mg and, in general, the results on the primary outcomes were consistent between the pooled and 80 mg group. In addition, the dose may have been reduced to 40 mg once daily to manage side effects and is not specified in the product monograph. However, only a few patients in the trial had a reduction in dose (i.e., four patients on placebo and two patients on tafamidis 80 mg).

A range of outcomes relevant to patients with ATTR-CM was evaluated in the trial, and the follow-up of 30 months was of adequate duration to assess mortality and changes in the KCCQ and 6MWT. Although the KCCQ and 6MWT have not been validated specifically for patients with ATTR-CM, they have been used in patients with heart failure, which impacts patients with ATTR-CM. The KCCQ has been validated in patients with congestive heart failure with an MCID of 5.7 for the overall score. The 6MWT test assesses the global function of organ systems involved in exercise. It is prone to a learning effect with repeated testing, which can result in improvements over time in the absence of any intervention, and is also impacted by patient motivation, encouragement, and cooperation. Such factors are anticipated to have affected the tafamidis and placebo groups equally and, therefore, would not have resulted in any systematic bias. The MCID for the 6MWT is 43 metres in patients with heart failure. In clinical practice, the HRQoL outcomes of the KCCQ and EQ-5D-3L are not routinely assessed and are primarily of research interest. Given that patients could be on tafamidis for longer than 30 months, the results of the open-label extension study of 60 months are awaited to determine the long-term safety profile of tafamidis.

Indirect Evidence

No indirect evidence was submitted by the sponsor. An independent literature search was conducted for indirect evidence by CADTH, but no studies were identified that met the inclusion criteria of the CDR review protocol.

Other Relevant Studies

The long-term open-label extension study (NCT02791230) for tafamidis is ongoing. The estimated enrolment for this study is 2,000 patients with wild-type or hereditary ATTR-CM.[28] Patients will receive tafamidis 61 mg (which is equivalent to tafamidis meglumine 80 mg; this formulation is available in the US) or, if not available, tafamidis meglumine 80 mg orally once daily for 60 months. Two cohorts are eligible for entry into this study: one cohort is patients who completed 30 months of the ATTR-ACT trial, and the second cohort is patients from specific countries who are diagnosed with ATTR-CM but who did not participate in ATTR-ACT. Patients with heart and/or liver transplant are not eligible for entry into the study. The anticipated completion date is December 7, 2024. The sponsor provided additional information to CADTH during the review process from an interim analysis for the ongoing extension study. These data suggest that treatment with tafamidis may offer a survival benefit compared with placebo, but this conclusion is speculative due to the paucity

of methodological detail available to assess the validity of these results. In the absence of more compelling long-term data, the durability of the treatment effect beyond 30 months remains inconclusive.

Discussion

Summary of Available Evidence

One study was included in this systematic review. The ATTR-ACT study was a phase III, double-blind RCT in adults with hereditary or wild-type ATTR-CM. A total of 441 patients were randomized in a 2:1:2 ratio to placebo, tafamidis 20 mg, or tafamidis 80 mg once daily for 30 months. Randomization was stratified by wild-type or hereditary ATTR-CM, and NYHA class I or class II/III. The primary outcome was a hierarchical combination of all-cause mortality and cardiovascular-related hospitalization at month 30 analyzed by the Finkelstein-Schoenfeld method. Key secondary outcomes were change from baseline to month 30 in the 6MWT and KCCQ overall score. Another secondary outcome was cardiovascular-related mortality, and exploratory outcomes were all-cause hospitalization, generic HRQoL, PGA, changes in NYHA classification, NT-proBNP, echocardiogram parameters, and mBMI. In the primary analysis, the 20 mg and 80 mg doses were pooled into a single group and, in exploratory analyses, the doses were examined individually. The trial was adequately powered for the primary outcome of all-cause mortality and had a duration of 30 months. The analyses for tafamidis 80 mg were exploratory and, therefore, conclusions based on statistical testing could not be made directly for this dose.

Interpretation of Results

Efficacy

Based on the Finkelstein-Schoenfeld analysis of the primary outcome, at month 30, more patients were alive in the pooled tafamidis group compared with placebo. The Finkelstein-Schoenfeld analysis for pooled tafamidis versus placebo demonstrated that at least one, or possibly both, outcomes (all-cause mortality and cardiovascular-related hospitalization) were statistically significantly different. Although the results of the tafamidis 80 mg dose group were exploratory, the findings were consistent with the finding in the primary analysis for the pooled tafamidis group. There were also more cardiovascular-related hospitalizations in the placebo group compared with the tafamidis 80 mg group, among patients who were alive at month 30. The clinical experts consulted for this review indicated that the mortality reduction observed in patients treated with tafamidis was clinically significant. The treatment effect of tafamidis was further supported by the finding that fewer cardiovascular-related deaths occurred in the tafamidis group than in the placebo group. In the exploratory subgroup analyses, the Finkelstein-Schoenfeld analyses for all-cause mortality and cardiovascular-related hospitalization were statistically significant for wild-type, heredity, and NYHA class I/II, but not for NYHA class III; this was consistent with the results from the primary analysis (except for the NYHA class III group).

HRQoL was measured using the KCCQ and was tested only if the primary outcomes and 6MWT results were statistically significant. For the key secondary outcome of KCCQ overall score, a statistically significant difference in favour of tafamidis was observed at month 30 between the pooled tafamidis and placebo groups, and this difference emerged as early as month 6 (but this time point was an exploratory analysis). In the exploratory analysis, the between-groups treatment difference also favoured for tafamidis 80 mg versus placebo. These estimates exceed the MCID of 5.7 for patients with congestive heart failure. In other exploratory analysis, the change from baseline to month 30 was smaller in the negative direction (indicating less worsening of health) for tafamidis 80 mg and tafamidis pooled compared with placebo for the KCCQ domains of physical limitation, symptom frequency, symptom burden, total symptoms, quality of life, social limitation, and clinical summary. For the KCCQ, the change from baseline to month 30 in the tafamidis pooled group was smaller in the negative direction (indicating less worsening of health) than in the placebo group for all subgroups; however, the subgroup analyses were exploratory.

Change in NYHA class was identified as an efficacy outcome of interest to this review. Although it appears that more patients in the pooled tafamidis group appeared to improve from class II to class I than in the placebo group, the change in NYHA class was an exploratory outcome measure in the ATTR-ACT trial.

Disability was measured as a key secondary outcome using the 6MWT and was part of the statistical testing hierarchy. A statistically significant difference in favour of tafamidis was apparent between the pooled tafamidis and placebo groups at month 30; this difference emerged as early as month 6 (but this time point was an exploratory analysis). The difference at month 30 in the 6MWT also favoured tafamidis 80 mg over placebo in an exploratory analysis. Although no MCID for the 6MWT test is available specifically for patients with ATTR-CM, these estimates exceeded the MCID of 43 metres for heart failure. For the 6MWT, the decrease in the distance walked from baseline to month 30 was smaller for tafamidis pooled compared with placebo in all subgroups. However, for patients with

NYHA baseline class III, the magnitude of the difference between placebo and tafamidis was smaller than the other subgroups; however, the subgroup analyses were exploratory.

Cardiac biomarkers (NT-proBNP) and echocardiogram parameters were exploratory outcomes in the ATTR-ACT study. According to the clinical experts, there is no defined decrease in the magnitude of NT-proBNP that is clinically important and stabilization of the baseline values, along with stabilization or improvement in other clinical assessments, would be considered an adequate response to treatment. In both the pooled tafamidis and placebo groups, NT-proBNP increased from baseline to month 30; however, the increase was smaller for the pooled tafamidis group compared with placebo. When interpreted with the data for all-cause and cardiovascular-related mortality, the NT-proBNP data support a cardiac benefit of treatment with tafamidis. Smaller magnitudes of changes were observed for GLS, LV end diastolic interventricular septal wall thickness, LV posterior wall thickness, and LVEF for the pooled tafamidis group compared with placebo.

Nutritional status (measure by mBMI) and need for heart or liver transplant were also efficacy outcomes identified in the CDR review protocol. The mBMI decreased from baseline to month 30 for both the pooled tafamidis group and placebo; however, the change was smaller for patients who received tafamidis. Clinical experts consulted for this review agreed that the mBMI is not used in clinical practice in Canada. Heart or combined heart/liver transplant were received by a similar proportion of patients in the placebo group, the tafamidis 80 mg group, and the pooled tafamidis group. CMAD implantation occurred in two patients who received tafamidis 80 mg and in no patients in the placebo group.

Harms

Almost all patients in the ATTR-ACT study experienced at least one AE, regardless of treatment group. The most common events were cardiac-related (i.e., atrial fibrillation and cardiac failure). Gastrointestinal effects, such as constipation, diarrhea, and nausea were also common, but experienced by a lower percentage of patients who received tafamidis than placebo. Urinary tract infection was experienced by more patients in the placebo group than in the tafamidis 80 mg group and the pooled tafamidis group.

A similar percentage of patients experienced at least one SAE in each of the placebo, tafamidis 80 mg, and pooled tafamidis groups. The most common SAEs were cardiac-related or aggravation of condition and were balanced between the groups. More patients in the placebo group stopped treatment due to AEs than in the tafamidis 80 mg or pooled tafamidis group; however, withdrawal from the study due to AEs was similar in all three groups.

In terms of notable harms, hypothyroidism was experienced by slightly more patients treated with tafamidis (in both the 80 mg and pooled groups) than in patients treated with placebo. More patients who received tafamidis had a thyroxine abnormality of less than 0.8 of the lower limit of normal. However, the clinical experts consulted for this review did not anticipate this to be of clinical significance and indicated that monitoring and management of thyroid abnormalities was relatively simple in clinical practice. Pruritis or rash occurred in more patients in the placebo group.

Other Considerations

The ATTR-ACT trial randomized patients to tafamidis 20 mg and tafamidis 80 mg. The 20 mg dose was included because it was studied for hATTR polyneuropathy and was shown to slow the progression of early stages of the disease, whereas the 80 mg dose was shown to cause more stabilization of the TTR protein in vitro.[34] The 80 mg dose is the one of relevance to this review, as it is the dose specified in the Health Canada product monograph. The primary analysis was conducted on the pooled tafamidis 20 mg and 80 mg dose group, whereas the analyses for the 80 mg dose were exploratory. The pooled group consisted of more patients on tafamidis 80 mg than 20 mg (i.e., 176 patients on 80 mg and 88 patients on 20 mg) and the available data for the 80 mg dose were in alignment with the data for the pooled group.

The ATTR-ACT trial was of 30 months duration, which was considered to be of sufficient duration to observe a difference in mortality, hospitalization, and changes in HRQoL and disability (measured by the KCCQ and 6MWT, respectively). Patients will likely be on lifelong tafamidis; the safety of tafamidis beyond 30 months will be informed by the long-term extension study for tafamidis, which is currently ongoing and includes sites in Canada. There is currently no comparative evidence with the available active treatment options for ATTR-CM, such as diflunisal, experimental treatments of doxycycline plus ursodiol and green tea extract, or heart/combined heart and liver transplantation. According to the clinical experts, these treatment options are used rarely, if at all, in patients with ATTR-CM, and the evidence for diflunisal is very limited.

Tafamidis 20 mg once daily has been approved as a treatment in several countries outside of North America for early stages of hATTR polyneuropathy.[34] In 2011, the European Medicines Agency approved tafamidis 20 mg once daily for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.[19] The evidence for the use of tafamidis for polyneuropathy comes from an 18-month double-blind RCT of tafamidis 20 mg once daily versus placebo in 128 patients with early-stage disease due to V30M mutation and a 12-month open-label extension of this study.[16] The FDA recently approved both tafamidis meglumine 80 mg and tafamidis 61 mg once daily (which is equivalent to tafamidis meglumine 80 mg) as a treatment for ATTR-CM.[20] The tafamidis 61 mg formulation is not marketed in Canada.

Conclusions

Based on a single double-blind, phase III RCT in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis was associated with reduced mortality and hospitalizations after 30 months compared with placebo. Clinically important differences were also observed in favour of tafamidis at month 30 in HRQoL and disability progression, as measured by the KCCQ overall score and 6MWT, respectively. Exploratory subgroup analyses suggested that treatment benefits are present for wATTR-CM, hATTR-CM, NYHA class I/II and NYHA class III, although the benefits for patients in NYHA class III are less clear. The most common AEs were cardiac-related (i.e., atrial fibrillation and cardiac failure). The most common SAEs were cardiac-related or aggravation of condition, and were experienced by a similar proportion of patients in the tafamidis and placebo groups. Thyroxine abnormality was higher in the tafamidis group, although this was anticipated to be of limited clinical significance. Further, the clinical experts consulted for this review agreed that tafamidis appears to be fairly well tolerated and monitoring requirements are anticipated to be minimal.

The current management strategy for ATTR-CM is primarily supportive cardiac disease treatments, as there are very few options available that target the underlying disease process. The only other TTR stabilizer used for the treatment of ATTR-CM in Canada is diflunisal; however, this is used beyond the Health Canada indication in this patient population, is associated with numerous limitations, and is not supported by rigorous evidence. There is no comparative evidence of tafamidis versus diflunisal; however, the clinical experts consulted for this review acknowledged that tafamidis appears to meet an unmet need for patients with wild-type and hereditary ATTR-CM.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	August 1, 2019
Alerts:	Bi-weekly search updates until project completion
Study types:	No filters were applied to limit retrieval by study type.
Limits:	Conference abstracts: excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	Registry number
.nm	Name of substance word
.ot	Original title
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

SYNTAX GUIDE	
1	(tafamidis* or Vyndamax* or Vyndaqel* or Vyndaquel* or UNII8FG9H9D31J or 8FG9H9D31J or fx1006* or fx 1006* or fx1005* or fx 1005* or fx006* or fx 006* or ZU7CF08A1A or UNIIZU7CF08A1A).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*tafamidis/
4	(tafamidis* or Vyndamax* or Vyndaqel* or Vyndaquel* or fx1006* or fx 1006* or fx1005* or fx 1005* or fx006* or fx 006*).ti,ab,kw,dq.
5	3 or 4
6	5 use oemezd
7	(conference abstract or conference review).pt.
8	6 not 7
9	2 or 8
10	remove duplicates from 9

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: tafamidis, Vyndaqel, Vyndamax	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: tafamidis, Vyndaqel, Vyndamax	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for search:	July 26–29, 2019
Keywords:	tafamidis, Vyndamax, Vyndaqel, fx 1006
Limits:	none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- internet search.

Appendix 2: Excluded Studies

Table 20: Excluded Studies

Reference	Reason for exclusion
Alexander KM, Evangelisti A, Witteles RM. Emerging Therapies for Transthyretin Cardiac Amyloidosis. *Curr Treat Options Cardiovasc Med.* 2019;21(8):40.[35]	Review
Cardenas-Soto K, Torres-Octavo B, Mendoza-Tejeda C, Fueyo-Rodriguez O, Dominguez-Rico C, Gonzalez-Duarte A. Quality of life assessment after 6 months of initiating treatment with tafamidis in patients with non-Val30Met mutations. Amyloid. 2019;26(sup1):57-58.[36]	Patient population
Emdin M, Aimo A, Rapezzi C, et al. Treatment of cardiac transthyretin amyloidosis: an update. Eur Heart J. 2019;20:20.[15]	Review
Falk RH. Tafamidis for transthyretin amyloid cardiomyopathy: the solution or just the beginning of the end? Eur Heart J. 2019;40(12):1009-1012.[34]	Review
Ferrer-Nadal A, Ripoll T, Uson M, et al. Significant reduction in proteinuria after treatment with tafamidis. Amyloid. 2019;26(sup1):67-68.[37]	Study design
Ishii T, Sekijima Y, Ando Y. Patient profile with ATTR-FAP and evaluation of the safety and efficacy of tafamidis meglumine in Japan - interim analysis in post-marketing surveillance. Amyloid. 2019;26(sup1):45-46.[38]	Study design
Lorenzini M, Elliott PM. Tafamidis for the treatment of transthyretin amyloidosis. Future Cardiol. 2019;15(2):53-61.[16]	Review
Manion C, Sharma UC. Tafamidis for Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2019;380(2):196.[39]	Letter to editor
Rigopoulos AG, Ali M, Abate E, et al. Advances in the diagnosis and treatment of transthyretin amyloidosis with cardiac involvement. Heart Fail Rev. 2019;24(4):521-533.[40]	Review
Le Bras A. Tafamidis: a new treatment for ATTR cardiomyopathy. Nature Reviews Cardiology. 2018;15(11):652.[41]	Review
Damy T, Judge DP, Kristen AV, Berthet K, Li H, Aarts J. Cardiac findings and events observed in an open-label clinical trial of tafamidis in patients with non-Val30Met and non-Val122Ile hereditary transthyretin amyloidosis. J Cardiovasc Transl Res. 2015;8(2):117-127.[42]	Patient population
Maurer MS, Grogan DR, Judge DP, et al. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. Circ Heart Fail. 2015;8(3):519-526.[43]	Study design
Merlini G, Plante-Bordeneuve V, Judge DP, et al. Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis. J Cardiovasc Transl Res. 2013;6(6):1011-1020.[44]	Study design

Appendix 3: Detailed Outcome Data

Table 21: All-Cause Mortality and Cardiovascular-Related Hospitalization (Per-Protocol Set)

	ATTR-ACT		
	Placebo N = 169	Tafamidis 80 mg N = 171	Pooled tafamidis N = 255
All-cause mortality			
Alive, n (%)	98 (58.0)	120 (70.2)	183 (71.8)
CV-related hospitalization			
Mean per patient per year[a]	0.87	1.02	0.99
Finkelstein-Schoenfeld P value	Reference	0.0002	< 0.0001

CV = cardiovascular.

[a] Among patients alive at month 30.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 22: All-Cause Mortality and Cardiovascular-Related Hospitalization (Sensitivity Analysis With Multiple Imputation, ITT Set)

	ATTR-ACT	
	Placebo N = 177	Pooled tafamidis N = 264
All-cause mortality		
Alive, n (%)	101 (57.1)	186 (70.5)
CV-related hospitalization		
Mean per patient per year	0.83	0.94
Finkelstein-Schoenfeld P value	Reference	0.0008

CV = cardiovascular; ITT = intention to treat.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 23: All-Cause Mortality and Cardiovascular-Related Hospitalization (Sensitivity Analysis Excluding Indeterminate Hospitalizations, ITT Set)

	ATTR-ACT	
	Placebo N = 177	Pooled tafamidis N = 264
All-cause mortality		
Alive, n (%)	101 (57.1)	186 (70.5)
CV-related hospitalization		
Mean per patient per year[a]	0.88	0.99
Finkelstein-Schoenfeld P value	Reference	0.0006

CV = cardiovascular; ITT = intention to treat.

[a] Among patients alive at month 30.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 24: All-Cause Mortality and Cardiovascular-Related Hospitalization (Sensitivity Analysis of Transplantation or CMAD Not Treated as Death, ITT Set)

	ATTR-ACT	
	Placebo N = 177	Pooled tafamidis N = 264
All-cause mortality		
Alive, n (%)	105 (59.3)	192 (72.7)
CV-related hospitalization		
Mean per patient per year[a]	0.88	1.0
Finkelstein-Schoenfeld P value	Reference	0.0003

CMAD = cardiac mechanical assist device; CV = cardiovascular; ITT = intention to treat.

[a] Among patients alive at month 30.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 25: All-Cause Mortality and Cardiovascular-Related Hospitalization at Month 30 for Subgroups (ITT Set)

	ATTR-ACT	
	Placebo	Pooled tafamidis
TTR genotype (wild-type)		
N	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]
CV-related hospitalization, mean per year[a]	[redacted]	[redacted]
Finkelstein-Schoenfeld P value	[redacted]	[redacted]
TTR genotype (hereditary)		
N	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]
CV-related hospitalization, mean per year[a]	[redacted]	[redacted]
Finkelstein-Schoenfeld P value	[redacted]	[redacted]
NYHA class I and II		
N	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]
CV-related hospitalization, mean per year[a]	[redacted]	[redacted]
Finkelstein-Schoenfeld P value	[redacted]	[redacted]
NYHA class III		
N	[redacted]	[redacted]
Alive, n (%)	[redacted]	[redacted]
CV-related hospitalization, mean per year[a]	[redacted]	[redacted]
Finkelstein-Schoenfeld P value	[redacted]	[redacted]

CV = cardiovascular; ITT = intention to treat; NYHA = New York Heart Association; TTR = transthyretin.

[redacted].

Source: Clinical Study Report for ATTR-ACT.[7]

Table 26: KCCQ (Pattern Mixture Analysis)

	ATTR-ACT			
	Total N	End of treatment time point (month 30)	Treatment group difference versus control	
		LS mean[a] change from baseline (SE)	LS mean difference (95% CI)	P value
Placebo	84[b]	−20.4 (1.9)	Reference	Reference
Pooled tafamidis	170[b]	−8.8 (1.5)	11.6 (7.5 to 15.8)	< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; MMRM = mixed model with repeated measures; SD = standard deviation; SE = standard error.

Note: The pattern mixture analysis used an MMRM ANCOVA with an unstructured covariance matrix (or as appropriate): study centre and the patient within the centre as random effects; treatment, visit, TTR genotype (variant and wild-type), pattern, visit by treatment interaction, and treatment by pattern interaction as fixed effects; and baseline score as covariate.[7]

[a] LS mean is from an MMRM ANCOVA model with random effects of the study centre and patient; fixed effects of treatment, visit, TTR genotype (wild-type or variant), pattern, visit by treatment interaction, and treatment by pattern interaction; and covariate of baseline score.

[b] Number of patients with KCCQ data at month 30.

Source: Clinical Study Report for ATTR-ACT.[7]

Table 27: KCCQ by Domain (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Physical limitation							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom stability							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom frequency							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom burden							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total symptoms							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Self-efficacy							

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean[a] change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality of life							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social limitation							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical summary							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; SD = standard deviation; SE = standard error.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Table 28: KCCQ Overall Score for Subgroups (ITT Set)

	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean change from baseline (SE)	N	LS mean difference (95% CI)	P value
TTR genotype (wild-type)							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTR genotype (hereditary)							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I and II combined							

	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD)	Mean (SD)	LS mean change from baseline (SE)	N	LS mean difference (95% CI)	P value
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; NYHA = New York Heart Association; SD = standard deviation; SE = standard error; TTR = transthyretin.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Table 29: Six-Minute Walk Test (Pattern Mixture Analysis)

	ATTR-ACT			
	Total N	End of treatment time point (month 30)	Treatment group difference versus control	
		LS mean[a] change from baseline (SE) (metres)	LS mean difference (95% CI)	P value
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Table 30: Six-Minute Walk Test at Month 30 for Subgroups (ITT Set)

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD) (metres)	Mean (SD) (metres)	LS mean change from baseline (SE)	N	LS mean difference (95% CI)	P value
TTR genotype (wild-type)							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTR genotype (hereditary)							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ATTR-ACT						
	Total N	Baseline	End of treatment time point (month 30)		Treatment group difference versus control		
		Mean (SD) (metres)	Mean (SD) (metres)	LS mean change from baseline (SE)	N	LS mean difference (95% CI)	P value
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class I and II combined							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA class III							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled tafamidis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; NYHA = New York Heart Association; SD = standard deviation; SE = standard error; TTR = transthyretin.

[redacted]

Source: Clinical Study Report for ATTR-ACT.[7]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MCID):

Table 31: Outcome Measures Included in Each Study

Outcome measure	Study ATTR-ACT (type of outcome, or analysis, such as primary or secondary)
6MWT	Key secondary analysis
KCCQ	Key secondary analysis
EQ-5D-3L	Exploratory analyses
PGA	Exploratory analyses
mBMI	Exploratory analyses
NT-proBNP	Exploratory analyses
Echocardiogram parameters (e.g., GLS, LV end diastolic interventricular septal wall thickness/LV wall thickness, and LVEF)	Exploratory analyses

6MWT = six-minute walk test; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; GLS = global longitudinal strain; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PGA = Patient Global Assessment.

Findings

Table 32: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
6MWT	A supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.	The 6MWT is a commonly used test to evaluate the global function of organ systems involved in exercise, namely, the heart, lungs, peripheral circulation, blood, nervous system, muscles, and bones and joints during walking, a self-paced activity.	43 metres for patients with heart failure.
KCCQ	A 23-item (15-question), disease-specific HRQoL questionnaire.	The KCCQ is a disease-specific HRQoL questionnaire used for patients with congestive heart failure.	• 5.7 points in KCCQ-os • 5.4 points for KCCQ-cs
EQ-5D-3L	A generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments.	The EQ-5D-3L has been extensively validated across countries around the world and in various conditions.	Unknown.
PGA	A scale used for global assessment of disease status by patients.	No information was found on the validity, reliability, and MCID of the PGA of disease status in ATTR-CM.	Unknown.
mBMI	• Measure of nutritional status, that takes into consideration hypoalbuminemia • mBMI = BMI × albumin	No validity information or MCID has been identified or proposed in ATTR-CM.	Unknown.

Outcome measure	Type	Conclusions about measurement properties	MCID
NT-proBNP	A marker of cardiac stress and injury. A cardiac biomarker that is released from the heart into the circulation in response to myocardial wall tension and stress.	NT-proBNP has been validated as a marker of cardiac stress and injury in patients with transthyretin amyloidosis (hereditary and wild-type).	Unknown.
Echocardiogram parameters (e.g., GLS, LV end diastolic interventricular septal wall thickness (mm), LV wall thickness, and LVEF)	A measure of cardiac LV systolic function.	An analysis of echocardiogram parameters (e.g., LV longitudinal strain, LV end diastolic interventricular septal wall thickness (mm), LV wall thickness, and LV ejection fraction) is a reliable examination commonly used in clinics.	Unknown.

6MWT = six-minute walk test; ATTR-CM = transthyretin-mediated amyloidosis cardiomyopathy; BMI = body mass index; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels version; GLS = global longitudinal strain; HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ-cs = KCCQ clinical summary score; KCCQ-os = KCCQ overall summary score; LV = left ventricular; LVEF = left ventricular ejection fraction; mBMI = modified body mass index; MCID = minimum clinically important difference; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; PGA = Patient Global Assessment.

6MWT

The 6MWT is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[45] The American Thoracic Society provides guidelines for the standardization of this test in order to maximize reliability.[45] Walk tests aim to evaluate the global function of organ systems involved in exercise, namely, the heart, lungs, peripheral circulation, blood, nervous system, muscles, and bones and joints during walking, a self-paced activity.[45] Walk tests were originally developed primarily to evaluate cardiopulmonary function in cardiac and pulmonary conditions (e.g., chronic obstructive pulmonary disease, heart failure, pulmonary hypertension).

6MWT MIDs for distances were reported for chronic obstructive pulmonary disease (54 metres)[45,46] and heart failure (43 metres).[45,47] Key limitations of these walk tests, especially in pediatric patients, include: a learning effect with repeated testing; confounding effect of patient motivation, encouragement, and cooperation; and impact of age, height, and weight on walk distance.[45] The learning effect could result in performance and detection bias (i.e., false-positive apparent benefits) when evaluating an intervention using these walk tests in a non-blinded, uncontrolled study. Additionally, differences in patient motivation, encouragement, and cooperation between assessments can impact walking distance by a magnitude similar to the effect of interventions,[48] which can produce substantial variability and be a source of performance bias in a non-blinded, uncontrolled study. Finally, previous studies have identified that age, height, and weight impact the distance travelled in six minutes,[49,50] which may affect the 6MWT results obtained from trials of longer duration.

A literature search was conducted to identify validation information and MIDs of the 6MWT in patients with cardiomyopathy due to TTR-mediated amyloidosis (ATTR-CM), wild-type or hereditary; none were identified.

KCCQ

The KCCQ is a self-administered, 23-item (15 questions), disease-specific HRQoL questionnaire that was originally developed in 2000 for use in patients with congestive heart failure.[31] The items of the KCCQ can be categorized into the following domains: physical limitation (question 1), symptoms (frequency [questions 3, 5, 7, 9], severity [questions 4, 6, 8], and recent change over time [question 2]), social limitation (question 16), self-efficacy (questions 11, 12), and quality of life (questions 13, 14, 15). All items are measured using a Likert scale with five to seven response options. Responses are scored using ordinal values, beginning with 1 for the response that implies the lowest level of functioning. Domain scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. Missing values within each domain are assigned the average of the answered items within the same domain. Two summary scores were defined in the original publication by Green et al.: a functional status score (combination of the physical limitation domain and symptom domain, excluding symptom change over time) and a clinical summary score (combination of the functional status score, quality of life domain, and social limitation domain).[31] The clinical summary score as defined by Green et al. is more commonly referred to as the overall summary score, and the functional status score is referred to as the clinical summary score.

The KCCQ was originally validated in patients with a clinical diagnosis of congestive heart failure and an ejection fraction of less than 40%.[31] A cohort of patients (n = 39; mean age, 64 years; 69% male; mean NYHA, 2.0 ± 0.59) with stable disease was used to assess the reliability of the KCCQ, while another cohort of patients (n = 39; mean age, 68 years; 62% male; mean NYHA, 3.3 ± 0.46) admitted to the hospital for congestive heart failure exacerbations was used to assess the responsiveness of the KCCQ. At baseline and at three months, each patient had their NYHA classification assessed, completed the KCCQ, the Minnesota Living with Heart Failure Questionnaire, and the Short Form (36) Health Survey (SF-36) questionnaires, and had a 6MWT administered. The convergent validity of each KCCQ domain and summary score was determined using baseline data from all patients and comparing this data with other measures that quantify similar concepts. The domains of the KCCQ generally showed high internal consistency, with Cronbach's alpha ranging from 0.62 for the self-efficacy domain to 0.90 for the physical limitation domain. The lower Cronbach's alpha for the self-efficacy domain may be due to the fact that it is composed of only two questions that acquire slightly different pieces of information. The Cronbach's alpha values for the KCCQ clinical summary and KCCQ overall summary were high (0.93 to 0.95). The KCCQ also showed good test–retest reliability, with mean changes of 0.8 points to 4.0 points for the various domains and summary scores over three months of observation, none of which were statistically significant. The KCCQ also exhibited high responsiveness, with responsiveness statistics ranging from 0.62 for the social limitation domain to 3.19 for the symptom domain. The responsiveness statistic for the KCCQ clinical summary was 2.77 and for the KCCQ overall summary was 1.74.[31]

There was no universally accepted gold standard for identification of functional status and quality of life in patients with heart failure at the time the KCCQ was developed, so the NYHA class, 6MWT, and domains from the Minnesota Living with Heart Failure Questionnaire and SF-36 questionnaires were used to validate the domain and summary scores of the KCCQ.[31] The physical limitation domain showed good correlation with NYHA class ($r = -0.65$) and with the distance walked in the 6MWT ($r = 0.48$). The symptom stability score was lower in patients admitted to the hospital than in those who were stable (25.8 versus 53.8). The symptom frequency and symptom severity domains correlated with

NYHA classification; the quality of life domain correlated with NYHA class (r =−0.64). The social limitation domain correlated with NYHA class and the SF-36 social limitation scale (r = 0.62). No adequate criterion standard was available for the self-efficacy domain, though domain scores were significantly lower in patients admitted to the hospital compared with stable outpatients (67.6 versus 83.5). Both the KCCQ clinical summary (F = 52.3) and KCCQ overall summary (F = 41.9) correlated with NYHA class, and baseline scores were significantly lower among patients who died or were rehospitalized than among those with event-free survival.

The KCCQ overall summary has been shown to be prognostic of subsequent cardiovascular mortality and hospitalizations in a cohort of patients with heart failure after a recent acute myocardial infarction (N = 1,516; mean age, 64 years; 73.6% male; 38.9% NYHA class I, 45.9% class II, 13.6% class III, 1.6% class IV).[51] Among those with higher KCCQ overall summary scores (≥ 75) the one-year event-free survival rate was 84% compared with 59% for those with lower scores (< 25).[51] In another cohort study (n = 1,358; mean age, 63.5 years; 73.9% male), a change in KCCQ overall summary was found to be linearly associated with cardiovascular mortality or hospitalization (hazard ratio [HR] for each five-point decrease in KCCQ overall summary: 1.12; 95% CI 1.07 to 1.18).[52] Associations of changes in KCCQ overall summary with clinical change was assessed in a North American cohort study (n = 476; mean age, 61 years; 75% male; 11% NYHA class I, 41% class II, 44% class III, 5% IV) in patients with heart failure and an ejection fraction of less than 40% by administering the KCCQ and other measures at baseline and week 6.[32] In this study, a mean improvement of 5.7 (SD, 16.1) points in the KCCQ overall summary was associated with a small improvement in heart failure from baseline as determined by a cardiologist's assessment of change using a validated change question (15-point Likert scale, from "extremely worse" to "extremely better" and grouped into categories of change). A mean decrease of 5.4 (SD, 10.8) points in the KCCQ overall summary was associated with a small deterioration in heart failure.[32]

Baseline data from a large RCT (N = 2,331; mean age, 59.1 years; 71.6% male; 63.4% NYHA class II, 35.7% class III, 1% class IV) was used to examine associations between the KCCQ domain and summary scores, and clinical indicators of disease severity, including the 6MWT and peak oxygen consumption (peak VO_2).[53] In this study, a one-point SD difference in 6MWT and peak VO_2 was found to be associated with a difference of approximately five points in the KCCQ overall summary and a difference of six points in the KCCQ clinical summary. The authors considered a one-point SD difference in 6MWT and peak VO^2 to represent a meaningful difference in heart failure patients, noting the criteria used for these indicators are more stringent than those used in previous studies.[53]

The KCCQ is considered a reliable and valid self-report instrument for measuring disease-specific quality of life in chronic heart failure.[30-32] The MCID was reported in the range of 5.4 to 5.7.[32] No validity information and no MCID has been identified or proposed in the ATTR-CM population.

The EQ-5D-3L

The EQ-5D-3L is a generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments.[54,55] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[54,55] The second part is a vertical, calibrated, 20 cm Visual Analogue Scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ VAS that best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported current health status based on the EQ VAS that is used to assess the overall health of the respondent rather than selected dimensions of individuals' health.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The EuroQol 5-Dimensions questionnaire has been extensively validated across countries around the world and in various conditions; however, no information on the validity of the EQ-5D-3L and no MCID was found specifically for ATTR-CM populations.

PGA

In the pivotal clinical study[7] included for this review, the study sites were provided with an approved translated version of the PGA questionnaire, which was used to assess patients' overall health status. At baseline, patients were asked to rate their current health on the PGA using seven response options that range from "normal, not at all ill" to "among the most extremely ill."[7] At follow-up visits, patients were asked to rate the change in their health status since baseline.[7] A higher score indicates a better overall condition.

A literature search was conducted to identify validation information and the MCID for the PGA in patients with ATTR-CM; none were identified.

mBMI

Patients with ATTR are affected by wasting; in those circumstances, BMI overestimates clinical status. A more accurate measure is the mBMI, which corrects for hypoalbuminemia and edema, and is calculated using the product of BMI and serum albumin.[56] Among 27 patients with hATTR in Sweden, the mBMI was strongly correlated with number of years before death (r = 0.89) and to the duration of gastrointestinal symptoms (r = −0.66).[57] The mBMI was also correlated with polyneuropathy disability score (P = 0.009).[57] Among 21 patients with hATTR who had a liver transplant, a preoperative mBMI of less than 700 kg g/L m^2 was associated with significantly lower overall survival compared with an mBMI of 700 kg g/L m^2 or higher after transplant (median survival, 5.2 months versus 78.8 months).[58] Another study compared the survival of patients with hATTR who received a liver transplant as part of an earlier series when severely malnourished patients were accepted (N = 34) and a later series of patients who were selected based on an mBMI above 600 kg g/L m^2 (N = 27) in Sweden.[59] Survival was significantly prolonged in the later series of patients who had an mBMI above 600 kg g/L m^2.[59]

No validity information and no MCID for mBMI has been identified or proposed in the ATTR-CM population.

NT-proBNP

NT-proBNP has been validated as a marker of cardiac stress and injury in patients with TTR amyloidosis (hereditary and wild-type) and light-chain amyloidosis.[60-65] Evidence has also shown that it is a valid surrogate marker for mortality in patients with hATTR.[64,65] The prognostic value of NT-proBNP has been well established for hospitalized patients with heart failure.[66]

In a large cohort study of 1,617 patients with TTR amyloidosis (1,452 with hereditary and 165 with wild-type), factors associated with survival were examined.[64] Over 1.2 years of follow-up, 115 patients died. Mortality rates increased with NT-proBNP quartile (Q1 = 1.7%, Q2 = 5.2%, Q3 = 21.7%, and Q4 = 71.3%). Patients with higher NT-proBNP quartile also presented with lower mBMI and renal function. NT-proBNP was weakly correlated with mBMI (r = −0.236), moderately correlated with left atrial diameter (r = 0.337), and strongly correlated with septal thickness (r = 0.654) and LV posterior wall thickness (r = 0.649). In the Cox proportional hazards model, the predictors of survival in patients with hereditary ATTR were age, mBMI, mutation (V30M), brain natriuretic peptide, and NT-proBNP (Q1 to Q3 pooled versus Q4). In 60 patients with hereditary ATTR of the Thr60Ala mutation, NT-proBNP was significantly associated with survival in univariate (HR = 0.39; 95% CI, 0.16 to 0.96 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) and multivariate (HR = 0.17; 95% CI, 0.03 to 0.92 for < 3,383 pg/mL versus ≥ 3,383 pg/mL) analyses.[65]

A prognostic staging system for patients with wild-type TTR amyloidosis was developed based on factors that affected overall survival.[67] Among 260 patients, multivariate predictors of mortality were age, ejection fraction, pericardial effusion, troponin, and NT-proBNP. The staging system included thresholds of 0.05 ng/mL for troponin and 3,000 pg/mL for NT-proBNP and stages were chosen based on association with death. The age- and sex-adjusted HR for NT-proBNP threshold of 3,000 pg/mL was 2.2 (95% CI, 1.36 to 3.60). The four-year overall survival estimates were 57% for stage 1 (both values below threshold), 42% for stage 2 (one value above threshold), and 18% for stage 3 (both values above threshold). Siepen et al. examined predictors of mortality in 191 patients with wild-type TTR amyloidosis.[68] In multivariable analysis, NT-proBNP was a predictor of mortality (HR = 1.0;

P = 0.018). Damy et al. examined predictors of mortality in 198 patients with cardiac amyloidosis (118 with light-chain amyloidosis, 57 with hereditary ATTR, and 23 with wild-type TTR amyloidosis).[69] In a multivariate analysis among the subset of patients with TTR amyloidosis, NT-proBNP was a significant predictor of mortality.

In another study of 79 patients with cardiac amyloidosis (26 with light-chain amyloidosis, 36 with hereditary ATTR, and 17 with wild-type ATTR), NT-proBNP significantly increased the risk of major adverse cardiac events (MACE) (HR = 8.00; 95% CI, 2.67 to 23.93).[63] The optimal cut-off value for predicting MACE was an NT-proBNP value of 4,000 pg/mL.[63]

No MCID information for NT-proBNP has been identified or proposed for ATTR-CM.

Echocardiogram Parameters

GLS

GLS (or LV GLS or LV longitudinal strain [LVLS]) is a measurement of global LV function from two-dimensional echocardiographic images.[70] A negative change indicates improvement, whereas a positive change indicates worsening of LV function. Global LV longitudinal systolic strain was assessed in 24 patients with light-chain amyloidosis.[71] Over a median follow-up of 487 days, global longitudinal strain was strongly correlated with higher NT-proBNP at baseline (r = −0.677). In univariate analysis, global longitudinal systolic strain was significantly associated with all-cause mortality (HR = 1.17; 95% CI, 1.02 to 1.35); however, statistical significance was lost in a multivariate model adjusted for age, gender, NYHA class, and high-dose melphalan with autologous stem cell transplantation (HR = 0.98; 95% CI, 0.67 to 1.45). In a larger study of 150 patients with light-chain amyloidosis (63 with cardiac amyloidosis and 87 without cardiac amyloidosis), GLS was a significant predictor of survival in a multivariate Cox model (HR = 2.68; 95% CI, 1.07 to 7.13 for GLS ≥ −14.81).[72]

In one study, LVLS was examined in 14 patients with hereditary ATTR with the V30M mutation (six with cardiac amyloidosis, four with extracardiac amyloidosis, and four without amyloidosis) and a control group of 14 healthy individuals without the mutation or cardiovascular disease.[73] The mean basal longitudinal strain, apical longitudinal strain (two chambers, three chambers, and four chambers), and mean longitudinal tension were all significantly higher (i.e., further from normal) compared with patients with extracardiac amyloidosis and, aside from the three-chamber longitudinal strain, these measures were also higher compared with patients who had the V30M mutation but no disease.

In another study conducted in 172 patients with cardiac amyloidosis (80 light-chain amyloidosis, 36 with hereditary ATTR, and 56 with wild-type ATTR), GLS was strongly correlated with LVEF (r = −0.55) and moderately correlated with LV wall thickness (r = 0.34).[74] In multivariable analysis, each incremental 1% increase in global LV longitudinal strain significantly increased the risk of mortality from any cause (HR = 1.1; 95% CI, 1.01 to 1.19).[74] In another study of 79 patients with cardiac amyloidosis (26 with light-chain amyloidosis, 36 with hereditary ATTR, and 17 with wild-type ATTR), LV longitudinal strain correlated with cardiac amyloid burden, as assessed with late gadolinium enhancement on cardiac magnetic resonance (correlation not provided) and as assessed histologically in three hearts (r = 0.72).[63] Siepen et al. examined predictors of mortality in 191 patients with wild-type ATTR and found that while GLS was a significant predictor in univariate analysis, it lost significance in multivariate analysis.[68]

The association between GLS and mortality was examined in 546 patients undergoing echocardiography for known or suspected LV impairment.[75] GLS was calculated from three standard apical views using 2D speckle tracking. Over a period of about five years, 91 patients died. GLS was significantly associated with mortality in nested Cox models (HR = 1.45; 95% CI, 1.19 to 1.77) and added to the predictive power of other clinical variables as measured by model χ2. The intraclass correlation coefficients for interobserver variability and intraobserver variability were 0.916 and 0.922, demonstrating good agreement.[75]

LV Wall Thickness and LV End Diastolic Interventricular Septal Wall Thickness

LV wall thickness, or LV end diastolic interventricular septal wall thickness, is assessed by echocardiogram to identify structural impairment due to cardiac remodelling. In 60 patients with hereditary ATTR of the Thr60Ala mutation, which causes cardiomyopathy as the predominant feature, LV posterior wall thickness was significantly associated with survival in univariate (HR = 0.42; 95% CI, 0.18 to 0.95 for < 17 mm versus ≥ 17 mm) and multivariate (HR = 0.17; 95% CI, 0.03 to 0.97 for < 17 mm versus ≥ 17 mm) analyses.[65] LV wall thickness progression was higher in patients who died compared with survivors (2.02 mm ± 0.85 mm per month versus 0.19 mm ± 0.03 mm per month).[76] Progression of LV wall thickness was associated with survival in univariate and multivariate analyses.[76] The evidence suggests that LV wall thickness is correlated with survival in patients with amyloidosis.

LVEF

LVEF is assessed by echocardiogram to measure systolic dysfunction. Patients with wild-type (N = 18) and V122I mutant (N = 11) TTR amyloidosis, which is a mutation that causes cardiomyopathy as the predominant feature of ATTR,[14] were prospectively evaluated every six months for up to two years by Ruberg et al.[8] An LVEF of less than 50% was significantly associated with mortality in univariate analysis (HR = 4.12; 95% CI, 1.24 to 13.6).[8]

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