Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende acoramidis til behandling af transthyretin amyloidose med kardiomyopati

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. acoramidis
2. Ansøgers endelige ansøgning vedr. acoramidis

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23.04.2025
DBS/ATN

Forhandlingsnotat

Dato for behandling i Medicinrådet	21. maj 2025
Leverandør	Bayer
Lægemiddel	Beyonttra (acoramidis)
Ansøgt indikation	Beyonttra (acoramidis) til behandling af transthyretin amyloidose med kardiomyopati
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Beyonttra (acoramidis):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke og pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Beyonttra	356 mg, 120 stk.	60.435,58	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, der gælder fra den 22.05.2025. [redacted] På denne måde er Beyonttra dækket af en aftale i samme periode som det konkurrerende lægemiddel Vyndaqel (tafamidis). Der er et forventet patentudløb på Vyndaqel november 2026.

Konkurrencesituationen

Beyonttra er det andet lægemidler som er godkendt **i** EMA til behandling af transthyretin amyloidose med kardiomyopati. Vyndaqel blev anbefalet af Medicinrådet til samme indikation i november 2024.

[redacted]

Tabel 2. Lægemiddeludgift for Beyonttra pr. patient

Lægemiddel	Styrke og pakningsstr.	Dosering	Pris pr pakning SAIP (DKK)	Lægemiddeludgift pr år (SAIP, DKK)
Beyonttra	356 mg, 120 stk.	712 mg 2 gange daglig, oral	[redacted]	[redacted]

Tabel 3: Lægemiddeludgift for Vyndaqel pr. patient

Trin	Lægemiddel	Styrke og pakningsstr.	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
[redacted]	Vyndaqel	61 mg, 30 stk.	61 mg daglig, oral	[redacted]	[redacted]
[redacted]	Vyndaqel	61 mg. 30 stk.	61 mg daglig, oral	[redacted]	[redacted]
[redacted]	Vyndaqel	61 mg, 30 stk.	61 mg daglig, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurderingen
England	Under vurdering	Link til vurderingen

Opsummering

[redacted]

Application for the assessment of Beyonttra® (acoramidis) for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) NYHA stage I – III with symptoms or a history of symptomatic disease

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
🟨	Confidential information
[Other]	[Definition of color-code]

Contact information

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Abbreviations

Abbreviation	Definition
6MWT	6-minute walk test
ACC	American College of Cardiology
ACM	All-cause mortality
AE	Adverse event
AF	Atrial fibrillation
AGM	Adjusted Geometric Mean
AHA	American Heart Association
AIP	Apotekets indkøbspris (pharmacy wholesale price)
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
ATTR-CM	Transthyretin amyloid cardiomyopathy
BIA	Budget impact analysis
BMI	Body mass index
BNP	Brain natriuretic peptide
cdf	Cumulative density function
CDSR	Cochrane Database of Systematic Reviews
CEC	Clinical events/endpoints committee
CENTRAL	Cochrane Central Register of Controlled trials
CFB	Change from baseline
CI	Confidence interval
CMA	Cost-minimization analysis

CMAD	Cardiac mechanical assist device
CMH	Cochran-Mantel-Haenszel
CMR	Cardiovascular magnetic resonance
CV	Cardiovascular
DMC	Danish Medicines Council
DSU	Decision Support Unit
eCFRs	Electronic case report form
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOCI	Event of clinical interest
EPAR	European public assessment report
EQ-5D-5L	EuroQoL 5-Dimension 5-Level Questionnaire
ESC	European Society of Cardiology
ESCHF	European Society of Cardiology-Heart Failure
ESS	Effective Sample Size
F-S	Finkelstein-Schoenfeld analysis
GLS	Global longitudinal strain
HCRU	Healthcare resource use
HF	Heart failure
HFSA	Heart Failure Society of America
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Hypothetical strategy
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
IPD	Individual patient data
ISA	International Society of Amyloidosis
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IXRS	Interactive voice/web response system
J2R	Jump to reference
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Summary
LS	Least squares
LTE	Long-term extension

LV	Left ventricular
MA	Meta-analysis
MAIC	Matching adjusted indirect comparison
mBMI	Modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
MI	Multiple imputation
mITT	Modified intention-to-treat
MMRM	Mixed model repeated measures
NA	Not available
N/A	Not applicable
NAC	National Amyloidosis Centre
NICE	UK's National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
OS	Overall survival
PET	Positron emission tomography
PICOS	Population, interventions and comparisons, outcomes, and study design criteria
PH	Proportional hazards
PK-PD	Pharmacokinetic/pharmacodynamic
PT	Preferred term
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomized clinical trial
RD	Risk difference
RRR	Relative risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form Health Survey
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

TTR	Transthyretin
ULN	Upper limit of normal
VAS	Visual analog scale
vATTR	Variant transthyretin amyloidosis
WHO	World Health Organization
wtATTR	Wild-type transthyretin amyloidosis

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	BEYONTTRA®
Generic name	Acoramidis
Therapeutic indication as defined by EMA	Expected EMA indication: Wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (1).
Marketing authorization holder in Denmark	BridgeBio Europe B.V. Weerdestein 97 Amsterdam, 1083 GG Holland
ATC code	C01EB25
Combination therapy and/or co-medication	N/A
(Expected) Date of EC approval	February 17th 2025
Has the medicine received a conditional marketing authorization?	N/A
Accelerated assessment in the European Medicines Agency (EMA)	N/A
Orphan drug designation (include date)	Orphan designation was granted by the European Commission in November 19, 2018. The sponsorship was transferred from Pharma Gateway AB (Sweden) to Bridge Bio Europe B.V. (Netherlands) in November 2021 (2).
Other therapeutic indications approved by EMA	N/A
Other indications that have been evaluated by the DMC (yes/no)	N/A
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Differences in clinical practice and number of patients in Scandinavia.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	356 mg film-coated tablets, available in a package of 120 tablets

2. Summary table

Summary	
Indication relevant for the assessment	Acoramidis is expected to be indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) NYHA stage I – III with symptoms or a history of symptomatic disease. Expected indication by EMA: Indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
Dosage regiment and administration	The recommended dose of acoramidis is 712 mg (two tablets of 356 mg) administered orally twice daily.
Choice of comparator	Vyndaqel® (tafamidis) is recommended by the DMC for wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). The recommended dose of tafamidis for patients with ATTR-CM is 61 mg taken orally once daily (3, 4).
Prognosis with current treatment (comparator)	ATTR-CM is a progressively, life-threatening condition associated with poor quality of life and survival, with median survival of approximately 2 years for vATTR and 5 years for wtATTR (5).
Type of evidence for the clinical evaluation	Matching-adjusted indirect comparison (MAIC)
Most important efficacy endpoints (Difference/gain compared to comparator)	Key MAIC results were: All-cause mortality: 28% reduction in the risk of death for acoramidis vs. tafamidis (HR: 0.719, [95%CI: 0.409, 1.264]). Results were not statistically significant. CV-related hospitalization: Statistically significant relative risk reduction of 34% in CV-related hospitalization for acoramidis vs. tafamidis (RRR: 0.663 [95% CI: 0.463, 0.948]) Change from baseline in NT-proBNP: No difference in NT-proBNP at month 30 between acoramidis and tafamidis (LS mean difference: 78.55, [95% CI: -1453.01, 1610.11])

Summary	
	Change from baseline in 6MWT: Statistically significant difference in 6MWT at month 30 for tafamidis vs. acoramidis (LS mean difference: -37.64 m [95% CI: -69.20, -6.07])
Most important serious adverse events for the intervention and comparator	Key MAIC results were: There were no statistically significant differences between acoramidis and tafamidis in any of the compared safety outcomes, except for "TEAEs related to the study treatment". Similarly, there were no statistically significant differences for severe TEAEs for acoramidis vs. tafamidis. There are no detailed data available on which TEAEs were considered severe.
Impact on health-related quality of life	Key MAIC results were: Change from baseline in KCCQ-OS: No statistically significant difference in KCCQ-OS at month 30 between acoramidis and tafamidis (LS mean difference: -3.41 [95% CI: -10.47, 3.66]) Health economic model: N/A. A cost-minimization model is presented.
Type of economic analysis that is submitted	Type of analysis: cost-minimization Type of model: N/A
Data sources used to model the clinical effects	N/A. The ITC demonstrated that acoramidis and tafamidis have similar clinical effect. Hence, a cost-minimization analysis is presented.
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	[redacted]
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Prevalence: 150 Annual increase in prevalence: 20
Budget impact (in year 5)	[redacted]

Abbreviations: 6MWT, 6-minute walk test; CV, Cardiovascular; DMC, Danish Medicines Council; EMA, European Medicines Agency; ITC, Indirect treatment comparison; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, Least squares; MAIC, Matching-adjusted indircet comparison; N/A, Not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QALY, Quality-adjusted life years; TEAE, Treatment-emergent adverse event; vATTR, variant transthyretin amyloidosis; wtATTR, wild-type transthyretin amyloidosis.

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

3.1 The medical condition

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease arising from the dissociation of transthyretin (TTR) tetramers into monomer or dimer components that can misfold and reform as amyloid fibrils in cardiac tissues which causes cardiac dysfunction, ultimately leading to HF and early death (6-8). The disease course is characterized by years of relatively stable clinical status, followed by substantial increase in severity of heart failure (HF) that becomes refractory to conventional treatment (8, 9). As ATTR-CM generally progresses slowly with minimal and nonspecific symptoms until advanced stage, diagnosis is often delayed or misattributed, resulting in patients having short life expectancy due to being in more advanced states of disease at diagnosis (6-8). ATTR-CM is distinct from HF alone and, when left untreated, is associated with a shorter duration of survival (2.5 to 3.6 years) that is less than half of that of patients diagnosed with HF (6 years) (10, 11).

There are two distinct forms of ATTR-CM: variant ATTR-CM (vATTR-CM), which arises from over 130 pathogenic variants in the TTR gene, and wild-type ATTR-CM (wtATTR-CM), in which the TTR misfolding is not related to a pathogenic variant but instead factors such as aging or oxidative stress (6, 7, 12). Wild-type ATTR-CM accounts for the majority of total ATTR-CM cases, with studies reporting between 63% and 86% of cases classified as wtATTR-CM (13-16). vATTR-CM has an earlier age of onset compared to wtATTR-CM: in an international, longitudinal, observational registry study (N=957; 2007 to 2011), the median age at onset of signs and symptoms was 71.4 years for patients with wild-type disease (n=67) compared to 39.0 years for patients with variant disease (n=885) (6, 8, 17).

As previously mentioned, the clinical presentation of ATTR-CM is typically associated with chronic HF and often includes nonspecific cardiovascular-related symptoms though non-cardiovascular symptoms have also been observed (Table 1) (18-20).

Diagnosing ATTR-CM is often challenging because of the nonspecific cardiac signs and symptoms, which can often lead to delayed diagnoses and/or misdiagnoses (18, 20). Hypertensive heart disease is a common misdiagnosis for patients with ATTR-CM (20).

Table 1 Common Cardiovascular and Non-cardiovascular Symptoms Associated with ATTR-CM

Common symptoms	
Cardiovascular	Non-cardiovascular
HF Arrhythmias Aortic stenosis Syncope or pre-syncope Angina Atrial fibrillation Shortness of breath Conduction system disease Cough Palpitations	Neurologic disorders (e.g., sensorimotor polyneuropathy, spinal stenosis, or carpal tunnel syndrome [often bilateral]) Autonomic disorders (e.g., orthostatic hypotension or urinary dysfunction) Gastrointestinal disorders (e.g., malabsorption) Musculoskeletal disorders (e.g., biceps tendon rupture) Visual disorders (e.g., vitreous opacities) Auditory disorders (e.g., full frequency hearing loss) Renopathy (e.g., proteinuria, renal failure)

ATTR-CM = transthyretin amyloid cardiomyopathy; HF = heart failure

Source: Bajwa 2022(21); Irabor 2022(22); Jain 2023(6); Jain 2023(23); Rimbas 2022(18); Rintell 2021(19); Witteles 2019 (20).

The severity of ATTR-CM is determined through National Amyloidosis Centre (NAC) ATTR Staging or by New York Heart Association (NYHA) class. Higher NYHA disease class or NAC stage are significantly correlated with a shorter duration of survival and a lower health-related quality of life (HRQoL), as measured by Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) and EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) scores (24-26).

As ATTR-CM progresses, an increase in ventricular wall thickness (caused by buildup of amyloid fibrils in the myocardium) may cause patients to develop HF-related symptoms including arrhythmias, commonly atrial fibrillation (AF) (6, 18, 20). Patients presenting with AF also experience an increased risk of thromboembolism, HF, renal dysfunction, diastolic dysfunction, and hemodynamic abnormalities (27). Continued buildup of amyloid fibrils may also lead to increased extracellular volume, reduced diastolic filling, and reduced stroke volume (7, 20, 28). Tachycardia may develop as the circulatory system increasingly depends on elevated heart rate to achieve circulation (5, 29).

Studies on survival rates in patients with ATTR-CM are limited (30). It is known that survival is worse with increasing NAC ATTR stage (5), in patients with vATTR-CM compared to wtATTR-CM (16), and substantially worse than compared with HF alone (10). A retrospective cohort study from 2022 concluded that all-cause mortality was significantly higher for ATTR-CM patients compared with matched HF patients in four Nordic countries. Specifically in Denmark, median survival was 25 (CI: 21, 30) months and 70 (CI: 53, NA) months for the ATTR-CM and HF cohort, respectively (10).

ATTR-CM is associated with a significant clinical and humanistic burden (5, 6, 18-23, 29, 31). The symptoms of ATTR-CM and the increasing burden patients experience as the disease progresses substantially impair patient HRQoL (e.g., including arrhythmias, reduced stroke volume and other physiological changes in the myocardium which may result in hospitalization) (5, 29, 31). The burden is further exacerbated by delays in diagnosis and misdiagnosis (18, 20). Additionally, ATTR-CM represents a significant economic burden both in direct costs to patients as well as healthcare resource use (HCRU) (5, 32-34). Overall, patients with ATTR-CM with more severe cardiovascular (CV)-related symptoms (as indicated by NYHA class) have greater healthcare costs, driven largely by the cost of hospitalization (32, 33).

3.2 Patient population

For wtATTR, the specialist committee of the Danish Medicines Council has estimated that the incidence is approximately 100 new patients per year (35) and the prevalence is 400-500 patients (3). These estimations have been confirmed during interviews with two Danish clinical experts (36, 37). Furthermore, ATTR-CM NYHA class I-III was considered to be comprised of approximately 100% of patients in Denmark (NHYA class IV is comprised of <1% of patients in Denmark) (37).

Table 2 summarizes incidence and prevalence data for ATTR-CM in Denmark.

Table 2 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	100	100	100	100	100
Prevalence in Denmark	400	450	500	550	600
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.
Abbreviations: N/A, Not applicable.
Source: (3, 35-37).

Table 3 presents the expected number of patients eligible for treatment with acoramidis in the coming years. These patient numbers were informed by Danish clinical expert opinion (36).

Table 3 Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2028
Number of patients in Denmark who are eligible for treatment in the coming years (NYHA I/III) - cumulative	150	170	190	210	230

Abbreviations: NYHA, New York Heart Association.
Source: (36).

3.3 Current treatment options

The current treatment algorithm in Denmark is divided into two pillars: 1) symptom-relieving treatment and prevention of complications; 2) disease-modifying treatments. The symptom-relieving therapies are aimed at treating heart failure (e.g. diuretics, thiazide, aldosterone antagonist), arrhythmia (e.g., amiodarone, beta blocker, calcium antagonists, digoxin), heart valve diseases (e.g., valve replacement), and extracardiac manifestations (e.g., treatment is dependent on which symptoms are present) (38).

In turn, disease-modifying treatments for ATTR include TTR stabilizers (e.g. tafamidis, acoramidis), TTR knockdowns (e.g. patisiran, vutrisiran, inotersen and eplontersen), and liver transplantation (38).

Tafamidis is approved by the EMA and indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). Tafamidis is also approved for a second indication: the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (4). Furthermore, tafamidis is currently reimbursed in Denmark for both these indications (3, 39). Information on acoramidis is provided in detail in Section 3.4.

At the moment of submission of this dossier, there were no TTR knockdowns approved by the EMA for the treatment of ATTR-CM. Historically, liver transplantation was the only disease-modifying treatment available to patients with ATTR-CM, but currently pharmacological disease-modifying treatments (e.g., tafamidis, patisiran [the latter is used off-label]) are preferred (38).

Despite current available treatments, ATTR-CM is a progressively, life-threatening condition associated with poor quality of life and survival, with median survival of approximately 2 years for vATTR and 5 years for wtATTR (5).

Finally, the presented treatment algorithm was considered relevant in Denmark by Danish clinical experts (36, 37).

3.4 The intervention

Acoramidis is a high-affinity TTR stabilizer, designed to mimic the disease-protective T119M variant, which has a unique ability to form hydrogen bonds between adjacent serine residues within the thyroxine-binding sites of the tetramer. Thus near-complete stabilization (>90%) of both wild-type or variant TTR is observed with acoramidis. This near-complete stabilization inhibits its dissociation into monomers, and thereby slows the amyloidogenic process that leads to cardiac tissue leading to transthyretin amyloidosis with cardiomyopathy (ATTR-CM) (40). An overview of the intervention is presented Table 4.

Table 4 Summary information on Beyonttra® (acoramidis)

Overview of intervention	
Indication relevant for the assessment	Acoramidis is expected to be indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult

Overview of intervention	
	patients with cardiomyopathy (ATTR-CM) NYHA stage I – III with symptoms or a history of symptomatic disease. Expected indication by EMA: Indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
ATMP	N/A
Method of administration	Oral administration
Dosing	The recommended dose of acoramidis is 712 mg (two tablets of 356 mg) administered twice daily.
Dosing in the health economic model (including relative dose intensity)	In the cost-minimization analysis, it was used the recommended dose of acoramidis, i.e., 712 mg (two tablets of 356 mg) administered orally twice daily.
Should the medicine be administered with other medicines?	N/A
Treatment duration / criteria for end of treatment	Continuous treatment
Necessary monitoring, both during administration and during the treatment period	N/A
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Treatment is to be used in patients with NYHA stage I – III. The NYHA functional class is a tool currently applied in Danish clinical practice (41, 42).
Package size(s)	356 mg film-coated tablets, available in a package of 120 tablets

Abbreviations: NYHA, New York Heart Association.
Source: (40)

3.4.1 The intervention in relation to Danish clinical practice

Acoramidis is a TTR stabilizer and is expected to be an additional disease-modifying treatment option for ATTR-CM within this category. The introduction of acoramidis could replace (partially) the use of tafamidis in Danish clinical practice.

3.5 Choice of comparator(s)

The relevant comparator in this submission is tafamidis, which is currently the only TTR stabilizer evaluated and recommended by the DMC for the treatment of patients with ATTR-CM. This choice is motivated by the similar clinical efficacy observed for acoramidis and tafamidis (presented in subsequent chapters of this application). Furthermore, tafamidis has also been considered the most relevant comparator for acoramidis in Danish clinical practice by Danish clinical experts (36, 37). Tafamidis was confirmed as an appropriate comparator in a dialogue meeting with the DMC. An overview of the comparator is presented in Table 5.

Table 5 Summary information on Vyndaqel® (tafamidis)

Overview of comparator	
Generic name	Tafamidis
ATC code	N07XX08
Mechanism of action	Tafamidis is a selective stabilizer of TTR. Tafamidis binds to the two thyroxine binding sites on the native tetrameric form of TTR, stabilizing the tetramer and preventing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in patients with TTR amyloid cardiomyopathy.
Method of administration	Oral administration
Dosing	The recommended dose of tafamidis for patients with TTR amyloid cardiomyopathy is 61 mg taken orally once daily.
Dosing in the health economic model (including relative dose intensity)	In the cost-minimization analysis, it was used the recommended dose of tafamidis (i.e., 61 mg taken orally once daily).
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Continuous treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	Treatment is to be used in patients with NYHA stage I – III. The NYHA functional class is a tool currently applied in Danish clinical practice (41, 42).
Package size(s)	Pack size: a pack of 30 x 1 soft capsules. Each soft capsule contains 61 mg of micronized tafamidis.

Abbreviations: NYHA, New York Heart Association; TTR, transthyretin.
Source: (43).

3.6 Cost-effectiveness of the comparator(s)

Tafamidis has been evaluated and recommended by the DMC for the treatment of patients with wild-type or variant transthyretin-mediated amyloidosis with cardiomyopathy. The recommendation only applies to patients who are in NYHA class I-III and NAC stage I or II (3).

Additionally, tafamidis has also been evaluated and recommended by the DMC for the treatment of patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy stage 1 (39).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

ATTRibute-CM study is divided in Part A and B. Part A assessed several efficacy outcomes at the end of 12 months of treatment (see Table 11), whereas Part B assessed several efficacy outcomes at the end of 30 months of treatment. The outcomes here described pertain to Part B, which is the relevant part of the study to this application.

Table 6 summarizes the primary efficacy endpoint from the ATTRibute-CM study. The primary efficacy endpoint was a hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization as adjudicated by the CEC, difference in change from baseline in NT-proBNP (≥ 500 pg/mL), and difference in change from baseline in 6MWD over a 30-month fixed treatment duration. As the primary efficacy outcome was a composite efficacy outcome, information on the individual efficacy outcomes (the majority of these were secondary efficacy outcomes) is also presented in Table 6 and considered relevant for this application.

It is important to mention that the primary efficacy endpoint outcomes from the ATTR-ACT trial was different than the one used in ATTRibute-CM. The primary endpoint in ATTR-ACT was a hierarchical combination of all-cause mortality, and frequency of cardiovascular-related hospitalizations over the duration of the trial, which is defined as the number of times a subject is hospitalized (i.e., admitted to a hospital) for cardiovascular-related morbidity (44). Hence, a comparison of primary efficacy endpoints was not possible.

Nonetheless, individual efficacy outcomes (on all-cause mortality and cardiovascular-related hospitalizations), as well as secondary outcomes (change from baseline in NT-proBNP and 6MWD) were available for the ATTR-ACT trial, which allowed a comparison with all individual efficacy outcomes that composed the primary efficacy endpoint from the ATTRibute-CM trial. Furthermore, both trials did collect data on the endpoint "hierarchical combination of all-cause mortality, and frequency of cardiovascular-related hospitalizations" (analyzed via win ratio), but these data were excluded from the ITC, because simulations have shown that the accuracy of an ITC-derived win ratio varied with the relative effect sizes of the treatments. Therefore, an ITC of the win ratio conducted using conventional methods based on aggregate data could be prone to bias (45). Hence, the comparative analyses of efficacy presented in Section 7 only shows results for the individual efficacy outcomes that compose the primary efficacy outcome of the ATTRibute-CM trial (presented in Table 6).

More information on the comparability between studies is provided in Section 6.1.2.

Table 6 Efficacy outcome measures relevant for the application (based on ATTRibute-CM trial)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary endpoint – not relevant to this application			
Hierarchical analysis of death from any cause, CV-hospitalization events, change from baseline in NT-proBNP levels and 6MWD[a] [ATTRibute-CM]	Month 30 (Part B)	Hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization as adjudicated by the CEC, difference in change from baseline in NT-proBNP (≥ 500 pg/mL), and difference in change from baseline in 6MWD over a 30-month fixed treatment duration.	The primary efficacy analysis will use the F-S test applied to a hierarchical combination of All-Cause Mortality, cumulative frequency of CV-related hospitalizations and CFB in 6MWT at the last available visit where both subjects have non-missing assessments over the 30-month duration for this analysis. The test is based on the principle that each subject is compared to every other subject within each stratum in a pair-wise manner. The hierarchical approach recognizes the greater importance of the mortality endpoint.
Individual efficacy outcomes – relevant to this application			
Change from baseline to Month 30 in 6MWD *****[ATTRibute-CM]	Month 30 (Part B)	Change from baseline to Month 30 in 6MWD	Data will be analyzed from the "Total distance walked by subject" fields on the "6 Minute Test at Baseline" and the "6 Minute Walk Test" at Month 30 visit eCFRs. Missing data due to reasons other than IMP discontinuation will be handled by mixed model repeated measures (MMRM) without imputation. For missing data following IMP discontinuation before the Month 30 visit and while subjects are alive, the primary analysis will utilize the Jump to Reference (J2R) multiple imputation (MI) approach.
Change from baseline to Month 30 in death from	Month 30 (Part B)	Any death, or death-equivalent (defined as receiving a heart transplant or a CMAD), recorded up to	Any death, receiving a heart transplant or a cardiac mechanical assist device (CMAD) recorded up to the 30-

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
any cause[b] [ATTRibute-CM]		the 30-month duration was summarized and analyzed as a time-to-event endpoint in the mITT population.	month duration will be summarized and analyzed as a time to event endpoint in mITT. The time to All-Cause Mortality will be analyzed using a stratified Cox proportional hazards model that includes treatment as an explanatory factor along with baseline 6MWT. P-values and confidence intervals for the HR will be based on the Wald statistic.
Cumulative frequency of CV-related hospitalization by Month 30 [ATTRibute-CM]	Month 30 (Part B)	Cumulative frequency of CV-related hospitalization by Month 30	Cumulative frequency of CEC adjudicated CV-related hospitalization will be analyzed using negative binomial regression analysis with treatment, the three stratification factors and an offset term equal to log each subject's study duration included in the model. Stratified Cochran-Mantel-Haenszel (CMH) row means scores tests will be used to analyze the frequency of CEC adjudicated cardiovascular-related hospitalizations by treatment.
Change from baseline to Month 30 in NT-proBNP[b] [ATTRibute-CM]	Month 30 (Part B)	Change from baseline to Month 30 in NT-proBNP	Similar analysis to 6MWT

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

[a] The primary efficacy is not used in this application, as the chosen method for the comparative analyses was not considered appropriate for a composite efficacy outcome.

[b] This outcome was the only exploratory efficacy outcome included in the analysis of the primary efficacy outcome.

Abbreviations: 6MWT, 6-minute walk test; CEC, Clinical events committee; CFB, change from baseline; CV, cardiovascular; eCFRs, electronic case report form; F-S, Finkelstein-Schoenfeld analysis; HR, Hazard ratio; IMP, Investigational medicinal product; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Source: (46, 47)

Validity of outcomes

The efficacy outcome measures from ATTRibute-CM (and ATTR-ACT, presented in Sections 6 and 7) are amongst the validated outcomes for clinical investigation of medicinal products for the treatment of acute heart failure by EMA. In these guidelines, EMA mentions acceptable primary endpoints to be, e.g., all-cause mortality (preferred), short term outcomes (focused on the patient’s symptoms), as well as composite endpoints (48).

The primary efficacy outcome from the trial ATTRibute-CM was the hierarchical analysis of death from any cause, CV-hospitalization events, change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and 6MWD.

The order of individual components in the hierarchical endpoint corresponds to their clinical impact. All-cause mortality and cumulative CV-related hospitalizations were considered to be the most clinically important components contributing to the overall clinical benefit-risk assessment within the hierarchical endpoint and were appropriately the first and second components in the hierarchy. NT-proBNP is an established, statistically significant univariate predictor of CV-related mortality and a reliable index of morbidity with respect to compensation status in chronic heart failure due to ATTR-CM (24, 49, 50). Inclusion of NT-proBNP into the morbidity category complemented the frequency of CV-related hospitalization events and was considered to be clinically relevant as the third component within the F-S test. The 6MWT is a well-established (51) functional measure of submaximal exercise tolerance that was considered to be clinically relevant as the final component of the hierarchical primary endpoint, and provided important evidence of the efficacy of acoramidis in participants with ATTR-CM with chronic heart failure.

According to EMA’s guidelines, compositive outcomes are often used as primary endpoints in clinical trials in heart failure and these may include various combinations of symptoms, signs, and of mortality or morbidity (48). Information on the individual efficacy outcomes is presented in Table 6, results for these are presented in Sections 6.1.4 (acoramidis) and 6.1.5 (tafamidis). The results of the comparative analyses of efficacy are presented in Sections 7.1.3 – 7.1.7.

Additionally, functional capacity was assessed using the 6-minute walk test (6MWT), which measures the distance a patient walks at their own pace on a level, hard surface in 6 minutes (52, 53). The 6MWT score correlates with quality of life (QoL) and prognosis in patients with ATTR-CM (52). There are currently no published data on the minimally clinical important difference in the 6MWT in ATTR-CM.

Finally, DMC has previously accepted similar efficacy endpoints/outcomes for the treatment of the same patient population in its assessment of tafamidis (3).

4. Health economic analysis

4.1 Model structure

A cost-minimization analysis (CMA) was deemed appropriate considering the available results from the matching-adjusted indirect comparison (MAIC), conducted on trial data from ATTRibute-CM (acoramidis) and ATTR-ACT (tafamidis). The MAIC showed similar efficacy and safety profiles for acoramidis and tafamidis (see Section 7 for more details).

4.2 Model features

Table 7 summarizes the model features for the presented CMA.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) NYHA stage I – III with symptoms or a history of symptomatic disease	Same population as presented in Section 3.2.
Perspective	N/A	This is a CMA.
Time horizon	1 year	The presented CMA shows a comparison on annual treatment acquisition cost between acoramidis and tafamidis.
Cycle length	N/A	This is a CMA.
Half-cycle correction	N/A	This is a CMA.
Discount rate	N/A	See above (Time horizon).
Intervention	Acoramidis	
Comparator(s)	Tafamidis	According to the *Dansk Cardiologisk Selskab holdningspapir 2024* on *Kardiel amyloidose* (38). Validated by Danish clinical experts (36, 37), as well as the DMC.
Outcomes	Annual treatment acquisition cost	The presented CMA shows a comparison on annual treatment acquisition cost between acoramidis and tafamidis.

Abbreviations: CMA, Cost-minimization analysis; N/A, Not applicable.

5. Overview of literature

5.1 Literature used for the clinical assessment

As ATTRibute-CM reported data on acoramidis vs. placebo, there was a need to conduct a literature search to identify efficacy and safety evidence for the most relevant comparator in Danish clinical practice. The literature search is described in detail in Appendix H. Table 8 lists the relevant literature included in this application.

Table 8 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Intervention - Acoramidis				
Data on file. Individual patient-level data from ATTRibute-CM (54)	ATTRibute-CM (pivotal trial) (55)	NCT03860935 (55)	Start: 19/03/2019 (55) Completion: 11/05/2023 (55) Data cut-off: 06/07/2023 (56)	acoramidis vs. placebo for patients with ATTR-CM (55)
Data on file. Clinical study report from ATTRibute-CM (46)	ATTRibute-CM (pivotal trial) (55)	NCT03860935 (55)	Start: 19/03/2019 (55) Completion: 11/05/2023 (55) Data cut-off: 06/07/2023 (56)	acoramidis vs. placebo for patients with ATTR-CM (55)
Results of the ATTRibute-CM trial and slides from the European Society of Cardiology Congress 2023, Amsterdam, 27 Aug 2023 (57)	ATTRibute-CM (pivotal trial) (55)	NCT03860935 (55)	Start: 19/03/2019 (55) Completion: 11/05/2023 (55) Data cut-off: 06/07/2023 (56)	acoramidis vs. placebo for patients with ATTR-CM (55)
Comparator - Tafamidis				
Full paper: Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail. Feb 2021;23(2):277-285 (58)	ATTR-ACT (59)	NCT01994889 (59)	Start: 09/12/2013 (59) Completion: 07/02/2018 (59) Data cut-off: 15/02/2018 (assumed same as EPAR) (60)	tafamidis vs. placebo for patients with ATTR-CM (59)

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
EMA EPAR Vyndaqel® (60)	ATTR-ACT (59)	NCT01994889 (59)	Start: 09/12/2013 (59) Completion: 07/02/2018 (59) Data cut-off: 15/02/2018 (assumed same as EPAR) (60)	tafamidis vs. placebo for patients with ATTR-CM (59)

* If there are several publications connected to a trial, include all publications used.

Abbreviations: ATTR-CM, Transthyretin amyloid cardiomyopathy; EMA; European Medicines Agency; EPAR, European public assessment report.

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

As ATTRibute-CM reported data on acoramidis vs. placebo, there was a need to conduct a literature search to identify HRQoL evidence for the most relevant comparator to Danish clinical practice. The literature search is described in detail in Appendix H (HRQoL was an outcome included in the clinical systematic literature review). Table 9 lists the relevant literature included in this application.

Table 9 Relevant literature included for documentation of health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file. Clinical study report from ATTRibute-CM (46)	Change in KCCQ-OS score from baseline to Month 30	Section 10 (individual and MAIC results)
Full paper Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin	Change in KCCQ-OS score from baseline to Month 30	Section 10 (individual and MAIC results)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail. Feb 2021;23(2):277-285 (58).		

Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; MAIC, matching-adjusted indirect comparison.

5.3 Literature used for inputs for the health economic model

Not applicable. This submission is based on a cost-minimization analysis. There were no further inputs used in the health economic analysis.

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Not applicable			

6. Efficacy

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

6.1.1 Relevant studies

Table 11 presents the studies used in the comparison of acoramidis vs. tafamidis. Efficacy data were presented for the modified intention-to-treat (mITT) population of ATTRibute-CM study (46). The mITT population was the primary analysis population for efficacy endpoints. The mITT population included participants who met the definition of ITT and had a baseline eGFR≥ 30 mL/min/1.73 m2. Participants in this population were analyzed according to their assigned randomized treatment (46). In turn, the intention-to-treat (ITT) population of ATTR-ACT study (60), which included patients with an eGFR≥25 mL/min/1.73 m^2 at screening. More information on this is provided in Section 6.1.2.1.

The data-cut for the results of the ATTRibute-CM trial was 06 July 2023 (follow-up time: 30 months of treatment; this data-cut was predefined) (46). In turn, the data-cut for the results of the ATTR-ACT trial was 15 February 2018 (follow-up time: 30 months of treatment; this data-cut was predefined) (44). The studies are described in more detail in Appendix A.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ATTRibute-CM. NCT03860935 (61)	30-month, randomized, double-blind, placebo-controlled study	Study Initiation/Completion: 19 March 2019/11 May 2023	Adult patients (≥18 to ≤90 years) with ATTR-CM (wild-type or variant), NYHA Class I to III symptoms, clinical HF with ≥1 previous hospitalization for HF or signs of volume overload or requiring diuretic treatment	Acoramidis 800 mg twice daily (ITT population: N=421; mITT population: 409)	Matched placebo (ITT population: N=211; mITT population: 202)	No formal efficacy interim analysis were planned. Predefined assessments were conducted after study participants had been on treatment for 12 months (Part A) and for 30 months (Part B) (47). Only the results for Part B are relevant to this application. Primary (56): Part A: CFB in 6MWT to month 12 of treatment Part B: Hierarchical combination of ACM and cumulative frequency of CV-related hospitalizations, CFB in the NT-proBNP, and CFB in 6MWT over a 30-month period Secondary (56): Part A: CFB in KCCQ-OS/TTR level/TTR stabilization to month 12 of treatment and safety Part B: CFB in 6MWT/KCCQ-OS/TTR level/TTR stabilization to month 30 of treatment A hierarchical combination of ACM and CV-related hospitalization over a 30-month period ACM, CV-related mortality, cumulative frequency of CV-related hospitalization by month 30, and safety

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ATTR-ACT (NCT01994889) (58)	RCT, Phase III, double-blind, multinational (13), multicenter (48)	Study Initiation/Completion: 9 December 2013/7 February 2018	Patients with variant or wild-type ATTR-CM	Tafamidis 80 mg (N=176) vs. Tafamidis 20 mg (N=88)	Placebo (N=177)	Primary: Hierarchical combination ACM and cumulative frequency of CV-related hospitalizations over the duration of the trial Secondary: CFB in 6MWT/KCCQ-OS to month 30, ACM, CV-related mortality, frequency of CV-related hospitalization, TTR stabilization at month 1, and safety No formal efficacy interim analysis were planned. Assessments were conducted after study participants had been on treatment for 30 months (predefined analysis) (44).

Note: The ATTR-ACT trial included also a tafamidis 20 mg arm. Data are not presented in this table as this posology was not relevant to this application.

Abbreviations: 6MWD, 6-minute walk distance; ACM, All-cause mortality; ATTR-CM, Transthyretin amyloid cardiomyopathy; CFB, Change from baseline; CV, cardiovascular; HF, Feart failure; ITT, Intention-to-treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; mITT, modified intention-to-treat; NYHA, New York Heart Association; proBNP, N-terminal prohormone of brain natriuretic peptide; RCT, Randomized clinical trial; TTR, transthyretin.

6.1.2 Comparability of studies

A feasibility assessment for the MAIC was performed through a review of the trial designs, eligibility criteria, outcome definitions, and population profiles to assess the similarities and differences between the ATTRibute-CM and ATTR-ACT trials and determine whether these differences could be adequately adjusted for in the MAIC analyses.

All cause-mortality (ACM) and CV-related hospitalizations were evaluated over 30 months in the ATTR-ACT and ATTRibute-CM trials. The change from baseline in 6MWT, NT-proBNP, and KCCQ-OS were evaluated over 12 and 30 months in the ATTR-ACT and ATTRibute-CM trials. ACM included heart transplant, cardiac mechanical assist device (CMAD) implantation or death in both trials (56).

A summary of the identified differences during feasibility assessment and how these were addressed is provided in this section.

6.1.2.1 Key Differences Between Study Designs

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[redacted]

[redacted]

[redacted]

[redacted]

6.1.2.2 Key Differences in Study Inclusion/Exclusion Criteria

[redacted]

[redacted]

6.1.2.3 Key differences in outcomes definitions

[redacted]

[redacted]

6.1.2.4 Key Differences in Definitions of CFB for Continuous Outcomes

[redacted]

6.1.2.5 Key Difference in Safety Outcomes

[redacted]

6.1.2.6 Comparability of patients across studies

Table 12 summarizes relevant baseline characteristics of patients included in the ATTRibute-CM and ATTR-ACT studies (before matching in the comparative analysis), including information on the most relevant effect modifiers (i.e., TTR genotype, NYHA class, NT-proBNP, age, and eGFR) (56).

In addition to the presented characteristics, patients were also compared regarding race, permanent pacemaker insert, implanted cardiac defibrillator, ethnicity, BMI, duration of ATTR-CM and baseline medications. The implanted cardiac defibrillator, ethnicity and BMI were considered similar between these populations (results before and after matching are shown in Appendix C.4.1).

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (before matching)

	ATTRibute-CM (mITT)		ATTR-ACT (ITT)	
	Acoramidis (N=421)	Placebo (N=211)	Tafamidis (80 mg) (N=176)	Placebo (N=177)
Age, median (Min, Max)	78.0 (50.3, 90.8)	78.0 (55, 91)	76.0 (46, 88)	74.0 (51, 89)
Gender, n (%)				
Male	384 (91.2)	186 (88.2)	158 (89.8)	157 (88.7)
Female	37 (8.8)	25 (11.8)	18 (10.2)	20 (11.3)
NYHA class, n (%)*				

	ATTRibute-CM (mITT)		**ATTR-ACT (ITT)**	
	Acoramidis (N=421)	**Placebo (N=211)**	**Tafamidis (80 mg) (N=176)**	**Placebo (N=177)**
I	51 (12.1)	17 (8.1)	16 (9.1)	13 (7.3)
II	293 (69.6)	162 (76.8)	105 (59.7)	101 (57.1)
III	77 (18.3)	32 (15.2)	55 (31.3)	63 (35.6)
NT-proBNP (pg/mL), median (Min, Max)*	2,326.0 (280, 15711)	2,306.0 (277, 8829)	3,122 (392.0, 22,020.1)	3,161 (298.0, 16,787.1)
6MWT (m), median (Min, Max)	362.68(150.6, 695.8)	348.87 (151.1, 598.4)	342.5 (61, 685)	346 (80, 822)
KCCQ-OS score, mean (SD)**	71.5 (19.4)	70.3 (20.5)	NA	65.90 (21.74)
Genotype, n (%)*				
vATTR	41 (9.7)	20 (9.5)	42 (23.9)	43 (24.3)
wtATTR	380 (90.3)	191 (90.5)	134 (76.1)	134 (75.7)

Note: The ATTR-ACT trial included also a tafamidis 20 mg arm. Data are not presented in this table as this posology was not relevant to this application.
*These baseline characteristics were considered different and were adjusted through weights in the MAIC.
**Overall Summary is the mean of the Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation scores.
Abbreviations: 6MWT, 6-minute walk test; ATTR, transthyretin amyloid; ATTR-CM, transthyretin amyloid cardiomyopathy; ITT, Intention-to-treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; SD, Standard deviation; vATTR, variant transthyretin amyloidosis; wtATTR, wild-type ATTR.
Source: (56).

The two trials had similar patient characteristics, except for the following large imbalances (≥10%):

- ATTRibute-CM enrolled fewer patients with mutant ATTR.
- ATTRibute-CM included fewer patients with NYHA class III.
- ATTRibute-CM enrolled patients with lower NT-proBNP (pg/mL) levels.
- ATTRibute-CM enrolled patients with a higher median age and higher proportion of patients aged ≥65 years (56).

Baseline characteristics that substantially differed between the trials included: baseline use of permanent pacemaker and baseline medications. Patients in ATTRibute-CM had a greater use of these medications at baseline and lower use of permanent pacemakers. Differences in these are not expected to impact the relative treatment effects because they are likely purely prognostic factors and not effect modifiers, as suggested by three global clinical experts (56).

Compared to the ATTR-ACT clinical trial population, the ATTRibute-CM clinical trial population appears to have less progressed disease likely due to earlier diagnosis and treatment (56).

It is currently recommended to match based on all known effect modifiers regardless of whether an imbalance exists (recommendation 4) (63) but not prognostic variables. This is done to ensure that balancing on one effect modifier won't disbalance another that was omitted from the matching. When it comes to matching on continuous covariates, matching on higher moments, such as the variance, has been shown to have no gain in terms of bias reduction, and in some scenarios, it even performed substantially worse than matching based only on the mean (64). Therefore, matching only on the mean and median was considered for continuous covariates (56). Several matching scenarios were tested and these are presented in Appendix C.1.1.1.

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

Table 13 summarizes the patient characteristics in the relevant population in Danish clinical practice. These data has been provided by a Danish clinical expert (37).

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (based on Danish clinical expert opinion (37))	Value used in health economic model
Age, median	80 years	N/A
Males, n (%)	NR	N/A
NYHA class, n (%)		
I	~25%	N/A
II	~50%	N/A
III	~25%	N/A
NT-proBNP (pg/mL), median	2,000	N/A
6MWT (m), median	NA	N/A
KCCQ-OS score, mean	65	N/A

Genotype, n (%)		
vATTR	1%	N/A
wtATTR	99%	N/A

Abbreviations: 6MWT, 6-minute walk test; ATTR, transthyretin amyloid; ATTR-CM, transthyretin amyloid cardiomyopathy; ITT, Intention-to-treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; mITT, modified intention-to-treat; NA, Not available; NR, Nor reported; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; vATTR, variant transthyretin amyloidosis; wtATTR, wild-type ATTR.
Source: (37).

6.1.4 Efficacy – results per ATTRibute-CM

Table 14 presents a summary of the efficacy results from the ATTRibute-CM trial, that have been published by Gillmore 2024 (61), Gillmore 2023 (65), Judge 2023 (66), and Judge 2024 (67). More information about the results of all outcomes included in the comparative analysis, as well as methods for each analysis are presented in Appendix B. The data presented here is the same data assessed by EMA. As mentioned in Section 6.1.1, the primary analysis population for efficacy endpoints in ATTRibute-CM was the mITT population.

Table 14 Main efficacy results – ATTRibute-CM study

ATTRibute-CM study – summary of efficacy results (mITT population)
Primary hierarchical analysis, acoramidis vs. placebo group • Win ratio: 1.8 (95% CI: 1.4, 2.2), p<0.001 Primary hierarchical analysis individual components, acoramidis vs. placebo group • Incidence of death from any cause, ARR, RRR: 6.4%, 25% (p=0.057)* • Incidence of CV-related hospitalisations per year, RRR: 0.496 (95% CI: 0.355, 0.695), p<0.0001 • NT-proBNP change from baseline to Month 30, ratio of adjusted geometric mean factor: 0.529 (95% CI: 0.463, 0.604), p<0.0001 • 6MWD change from baseline to Month 30, least-squares mean difference, metres: 39.6 (95% CI: 21.1, 58.2), p<0.0001

*Kaplan-meier is presented in Appendix B.
Abbreviations: 6MWD, 6-minute walk distance; CI, Confidence interval; CV, cardiovascular; proBNP, N-terminal prohormone of brain natriuretic peptide; RRR, Relative risk ratio
Source: Gillmore 2023(65); Gillmore 2024(61); Judge 2023(66), Judge 2024(67).

It is also important to note that the ACM benefit observed in month 30 (Table 14) was maintained until month 42, as observed in a recent publication reporting on initial results from the open-label extension of the ATTRibute-CM trial (results shown in more detail in Appendix B) (68).

The proportion of patients that discontinued the study was 20.8% (n=85) in the acoramidis arm, and 25.7% (n=52) in the placebo arm, in the ATTRibute-CM study. Reasons for study discontinuation were withdrawal of consent (acoramidis, n[%]: 15

[3.7%] vs. placebo, n[%]: 5 [2.5%]), and death (acoramidis, n[%]: 70 [17.1%] vs. placebo, n[%]: 47 [23.3%]) (46).

6.1.5 Efficacy – results per ATTR-ACT

Table 15 presents a summary of the efficacy results from the ATTR-ACT trial, that have been published by Damy et al., 2021 (58) and in the EMA EPAR for Vyndaqel® (60). More information about the results of all outcomes included in the comparative analysis, as well as methods for each analysis are presented in Appendix B. The data presented here is the same data assessed by EMA.

Table 15 Main efficacy results – ATTR-ACT study

ATTR-ACT study – summary of efficacy results (ITT population)
Primary analysis (hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations), tafamidis vs. placebo group: • p-value from F-S method *P* = 0.0030 (meaning a significant reduction in all-cause mortality and CV-related hospitalizations compared with placebo)
Primary hierarchical analysis individual components, tafamidis vs. placebo group: • ACM, expressed as a HR (95%CI): 0.690 (0.487–0.979), p=0.0378* • Incidence of CV-related hospitalisations per year, relative risk ratio (95%CI): 0.70 (0.57–0.85), p=0.0005
NT-proBNP • NT-proBNP change from baseline to Month 30, least-squares mean difference (SE): -2587.54 (570.248), p<0.0001
6MWT • 6MWD change from baseline to Month 30, least-squares mean difference, metres: 75.77 (10.08), p<0.0001

*Kaplan-meier is presented in Appendix B.

Abbreviations: 6MWT, six-minute walk test; ACM, all-cause mortality; CI, Confidence interval; CV, cardiovascular; F-S, Finkelstein-Schoenfeld analysis; HR, Hazard ratio; ITT, Intention-to-treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; LS, least squares; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; SE, standard error.

Source: Damy et al., 2021(58), EMA EPAR (60).

According to the EPAR data, there were 21.6% patients (n=38) discontinuing tafamidis 80 mg and 30.5% of patients (n=54) discontinuing placebo, during the ATTR-ACT study. Reasons for discontinuation were not publicly available. However, deaths were recorded in 14.2% of patients (n=25) in the tafamidis 80 mg arm and in 21.5% of patients (n=38) in the placebo arm (60).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Outcome definition differences and how these were addressed are presented in Sections 6.1.2.3, 6.1.2.4 and 6.1.2.5.

7.1.2 Method of synthesis

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7.1.3 Results from the comparative analysis

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.1.4 Efficacy – results per ACM

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[redacted]

7.1.5 Efficacy – results per cumulative frequency of CV-related hospitalization

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

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7.1.6 Efficacy – results per change from baseline in NT-proBNP

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

7.1.7 Efficacy – results per change from baseline in distance walked during the 6MWT

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

[redacted]

[redacted]

8. Modelling of efficacy in the health economic analysis

This chapter is not applicable since a CMA was conducted.

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

Not applicable.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 22 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A

Method/approach	Description/assumption
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

Not applicable.

Table 23 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference

Disease-free survival	Recurrence	N/A
	Death	N/A
Recurrence	Death	N/A
Health state/Transition		N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

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

Not applicable.

Table 24 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Table 25 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]

[Intervention]	N/A	N/A	N/A
[Comparator]	N/A	N/A	N/A

9. Safety

This section presents a comparative analysis of the available safety data for the ATTRibute-CM and ATTR-ACT trials.

9.1 Safety data from the clinical documentation

The safety population in the ATTRibute-CM trial included all randomized subjects who received at least one dose of investigational medicinal product (IMP). Safety analyses were presented by actual treatment received (47). The safety population in the ATTR-ACT trial included all subjects who were enrolled (randomized) and received at least 1 dose of double-blind medication (44).

All adverse events included in the adverse event summaries are treatment emergent adverse events (TEAEs). Furthermore, serious TEAE was defined as subjects who had at least one treatment emergent serious adverse event (SAE) meeting a seriousness criterion (death, life threatening, requires or prolongs hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition). In turn, severe TEAE was defined as subjects who had at least one TEAE with a severity of severe (47).

[redacted]

[redacted]

[redacted]

Table 26 Overview of safety events (30 months of treatment)

	ATTRibute-CM			ATTR-ACT			ITC
	Acoramidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	Tafamidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	[redacted]
Number of adverse events[a], n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of serious adverse events*[a], n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ATTRibute-CM			ATTR-ACT			ITC
	Acoramidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	Tafamidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ATTRibute-CM			ATTR-ACT			ITC
	Acoramidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	Tafamidis [redacted]	Placebo [redacted]	Difference, % (95 % CI)	[redacted]
Number and proportion of patients who had a dose reduction[b], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ATTRibute-CM			ATTR-ACT			ITC
	Acoramidis [redacted]	**Placebo** [redacted]	**Difference, % (95 % CI)**	**Tafamidis** [redacted]	**Placebo** [redacted]	**Difference, % (95 % CI)**	[redacted]
adverse events[a], n (%)							
Additional available safety data							
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TESAE related to study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITC, indirect treatment comparison; OR, odds ratio; RD, risk difference; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

[a] Adverse event refers to treatment-emergent adverse event. Proportion of patients are also presented.

[b] Patients with dose reduced due to TEAEs.

* Risk Difference (95% CI)

There are no comparative analyses on specific serious adverse events with frequency of ≥ 5% recorded. A list of all serious adverse events observed in the studies separately was reported in Appendix E. In the same Appendix, a list of common TEAEs analyzed in the MAIC in both trials is also presented (Table 55 in Appendix C.4.2).

Table 27 Serious adverse events (time point)

Adverse events	Intervention (N=x)		Comparator (N=x)	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Adverse event, n (%)				
Not reported				

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Safety data showed that there were no statistically significant differences between acoramidis and tafamidis. Therefore, a CMA model is presented in this application and this subsection is considered not applicable.

Table 28 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)				
Not applicable				

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

The comparative analyses on safety data are informed by the ATTRibute-CM and ATTR-ACT trials and results are presented in Section 9.1. No further data from external literature is presented in this section.

Table 29 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	Not applicable							

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

The ATTRibute-CM trial collected EQ-5D-5L with UK-specific tariffs, whereas in the ATTR-ACT trial, EQ-5D-3L data with US-specific tariffs were collected. The MAIC did not compare these data because the ATTR-ACT trial only reported EQ-5D data for the pooled tafamidis dosing regimen. Hence, these data were not included in this application. However, available data for both trials separately are presented in Appendix F.

Additionally, these studies have collected HRQoL using the KCCQ-OS, which is presented in Table 30 and Section 10.1.

Table 30 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L (UK tariffs)	ATTRibute-CM	Comparison was not possible. Data were not included in this application, but results shown in Appendix F.1.
EQ-5D-3L (US tariffs)	ATTR-ACT	Comparison was not possible. Data were not included in this application, but results shown in Appendix F.2.
KCCQ-OS	ATTRibute-CM and ATTR-ACT trials	Included in this application. Purpose is to show similar clinical effectiveness between acoramidis and tafamidis

Abbreviaitons: HRQoL, Health-related quality of life; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary.

10.1 Presentation of the health-related quality of life [KCCQ-OS]

10.1.1 Study design and measuring instrument

The KCCQ is a self-administered questionnaire (divided into seven domains) developed to measure patients' perception of health status and HRQoL in patients with heart failure. Items included heart failure symptoms, impact on physical and social functions, and how their heart failure impacted QoL (46).

The KCCQ-OS ranges from 0 to 100, with higher scores indicating better health status and QoL. Correlation between the KCCQ domains and other heart failure assessments (eg, 6MWD or NYHA Class) have been reported, and the KCCQ was found to be a valid, reliable, and responsive health status measure for patients with congestive heart failure (70).

The KCCQ has been adopted as a common assessment in studies of heart failure interventions and is an independent predictor of survival in heart failure (71). The KCCQ-OS has been shown to rapidly and consistently decline over time in patients with ATTR-CM, making it an effective measure of patients' perception of health status (5, 51). A KCCQ-OS change of five or more points has been shown to be clinically significant and independent predictor of reduced mortality and reduced CV-related hospitalization in patients with chronic heart failure (72, 73).

10.1.2 Data collection

The KCCQ-OS was administered on Day 1, and again every 3 months through Month 12 and then every 6 months through Month 30. Participants who prematurely discontinued the study had the KCCQ-OS administered at the time of discontinuation (46).

The KCCQ-OS values were calculated from the answers on the “Kansas City Cardiomyopathy Questionnaire” electronic case report form (eCRF) according to the Scoring Instructions provided by Outcomes Instruments, LLC (46). The scoring algorithm adjusts for missing answers to questions by calculating means of questions actually answered. The algorithm also specifies the minimum number of responses required to calculate each summary score (47).

For missing data following study drug discontinuation before the Month 30 visit and while participants were alive, the key analysis utilized the jump to reference (J2R) multiple imputation approach (46).

Least squares means were displayed for each postbaseline study visit to summarize treatment effects over time. Summary statistics of the overall score, the seven domain scores, the Total Symptom Score and the Clinical Summary Score were presented by treatment group and visit (46).

The changes from baseline to Month 30 for KCCQ-OS were analyzed using the mixed model repeated measures (MMRM) from the key analysis without imputation of missing values (46).

The number and percentage of participants with net increase in KCCQ-OS (change from baseline > 0) at Month 30 were summarized. Participants with missing change from baseline at Month 30 were imputed as not meeting the definition of net increase. Stratified Cochran-Mantel-Haenszel (CMH) based on the imputed data with stratification factors of genotype, NT-proBNP level, and eGFR level from interactive voice/web response system (IXRS) was performed (46). Table 31 presents the pattern of missing data and completion for the analysis of the KCCQ-OS.

Table 31 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	409	NR	NR	408 (NR)
Month 3	409	NR	NR	263 (NR)
Month 6	409	NR	NR	389 (NR)
Month 9	409	NR	NR	390 (NR)
Month 12	409	NR	NR	397 (NR)
Month 18	409	NR	NR	404 (NR)
Month 24	409	NR	NR	407 (NR)
Month 30	409	NR	NR	405 (NR)

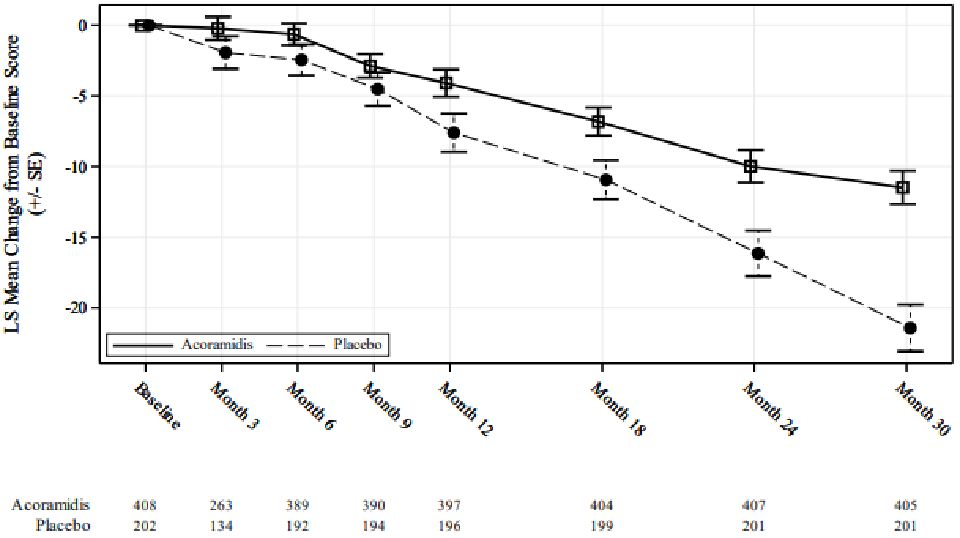
Note: Missing measurements due to early discontinuation of study drug were imputed using the J2R method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values. Ns represent both observed and imputed data points.
Abbreviations: NR, Not reported
Source: (46)

10.1.3 HRQoL results

10.1.3.1 ATTRibute-CM results

The results from the KCCQ-OS for acoramidis are summarized in Figure 5 and Table 32. In Figure 5, a treatment effect for change from baseline in KCCQ-OS favoring acoramidis was observed early, with the curves starting to separate at Month 3, and separation increasing in magnitude through Month 30 (prespecified analysis) (46).

Figure 5 Least Squares Mean (+/- SE) Change From Baseline in KCCQ-OS Over Time (with J2R), mITT Population



Abbreviations: vATTR-CM, variant ATTR-CM; wtATTR CM, wild-type ATTR-CM; eGFR, estimated glomerular filtration rate; J2R, Jump to Reference; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SE, standard error Notes: The change from baseline in KCCQ-OS was analyzed using the MMRM with treatment group, visit, genotype (vATTR-CM versus wtATTR-CM), NT-proBNP level (≤ 3000 versus > 3000 pg/mL), eGFR level (≥ 45 versus < 45 mL/min/1.73 m2) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study drug were imputed using the J2R method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values. Ns represent both observed and imputed data points.
Source: (46).

At Month 30, a statistically significant (p < 0.0001) and clinically meaningful treatment benefit on KCCQ-OS was observed favoring acoramidis, with a 10 point increase from baseline LS mean difference observed between the two treatment groups (Table 32) (46).

Table 32 HRQoL [KCCQ-OS] summary statistics

	Acoramidis		Tafamidis		Acoramidis vs. Tafamidis
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Month 30 (change from baseline)	405	-11.48 (1.181)	201	-21.42 (1.651)	LS Mean difference (SE): 9.94 (2.024) 95% CI: 5.97, 13.91 p-value: <0.0001

Note: Mean here is Least Squares Mean.
Abbreviations: CI, Confidence interval; LS, Least Squares; SE, Standard error.
Source: (46).

10.1.3.2 ATTR-ACT results

Results for the KCCQ-OS from the ATTR-ACT trial are available in the Damy et al. 2021 publication (58). The change from baseline to Month 30 in KCCQ-OS score showed a reduction in decline in patients treated with both tafamidis 80 and 20 mg compared with placebo [LS mean (SE), 13.48 (2.20) and 13.99 (2.96), respectively, p<0.0001 for both] (58).

10.1.3.3 MAIC results

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

[redacted]

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

Not applicable. A CMA is presented in this submission.

10.2.1 HSUV calculation

Not applicable.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Not applicable.

Table 34 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable.				

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

Not applicable. A CMA is presented in this submission.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 35 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable.				

Table 36 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable.				

11. Resource use and associated costs

The “Key figures including general mortality” were included in the CMA, however the “General Mortality” sheet was excluded as there was no mortality data included in the analysis. In the presented CMA, there was a cost comparison of annual treatment acquisition costs between acoramidis and tafamidis. No other cost was included in the analysis, as no other cost category was expected to differ between acoramidis and tafamidis.

11.1 Medicines - intervention and comparator

The apotekets indkøbspris (AIP; pharmacy wholesale price) used in the CMA for acoramidis was [redacted] and for tafamidis was DKK 60,435.58 (the available AIP in medicinpriser.dk for the strength of 61 mg and pack size of 30 capsules (74)). Tafamidis is also available in a strength of 20 mg and package size of 30 capsules, however this strength is not reimbursed for the treatment of patients with ATTR-CM.

Both medicines are administered orally, so it was assumed there is no wastage nor vial sharing, and relative dose intensity is assumed to be 100%. Furthermore, these treatments are assumed to be continuous treatments.

Table 37 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Acoramidis	1,424 mg (daily)	100% (assumed)	Daily	No
Tafamidis	61 mg (daily)	100% (assumed)	Daily	No

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Not applicable. Both acoramidis and tafamidis are administered orally so the administration cost is assumed to be DKK 0.

Table 38 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.4 Disease management costs

Not applicable. Disease management costs are assumed to be the same for acoramidis and tafamidis.

Table 39 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Not applicable				

11.5 Costs associated with management of adverse events

Not applicable. Acoramidis and tafamidis shared a similar safety profile, hence costs associated with management of adverse events were assumed to be the same.

Table 40 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Not applicable		

11.6 Subsequent treatment costs

Not applicable.

Table 41 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Not applicable				

11.7 Patient costs

Not applicable.

Table 42 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Not applicable	

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

Not applicable.

12. Results

12.1 Base case overview

The base case results of the CMA are summarized in Table 43.

Table 43 Base case overview

Feature	Description
Comparator	Tafamidis
Type of model	Cost-minimization analysis
Time horizon	1 year
Treatment line	N/A
Measurement and valuation of health effects	N/A. Health effects were not explored in the model due to the chosen model type.
Costs included	Medicine acquisition costs (annual)
Dosage of medicine	Based on the SmPC of acoramidis and tafamidis (4, 40)
Average time on treatment	These are continuous treatments, so it was assumed patients take the recommended daily dose every day for a year.
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No. No wastage is expected as both acoramidis and tafamidis are administered orally
Average time in model health state Health state 1 Health state 2 Health state 3 Death	N/A

Abbreviations: N/A, Not applicable; SmPC, Summary of Product Characteristics.

12.1.1 Base case results

The base case results from the CMA are presented in Table 44. The annual treatment acquisition cost difference for acoramidis, compared to tafamidis, was [redacted].

Table 44 Base case results, discounted estimates (DKK)

	Acoramidis	Tafamidis	Difference
Medicine acquisition costs (annual)	[redacted]	735,803.19	[redacted]
Total costs	[redacted]	**735,803.19**	[redacted]
Total life years	**N/A**	**N/A**	**N/A**
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

As the presented model is a CMA, both deterministic sensitivity analyses and probabilistic sensitivity analyses were considered not applicable. Discount price scenarios are however presented.

12.2.1 Deterministic sensitivity analyses

Not applicable.

Table 45 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Not applicable					

Scenario analyses

Two scenarios on price discount were tested and results are presented in Table 46.

Table 46 Scenario analyses

Scenario	Description	Annual treatment	Annual treatment	Incremental costs (DKK)

		acquisition cost for acoramidis (DKK)	acquisition cost for tafamidis (DKK)	
Base case	-	[redacted]	735,803.19	[redacted]
Price discount to AIP for Beyonttra®	[redacted] discount on Beyonttra®	[redacted]	735,803.19	[redacted]
	[redacted] discount on Beyonttra®	[redacted]	735,803.19	[redacted]

12.2.2 Probabilistic sensitivity analyses

Not applicable, as this is a CMA with very little uncertainty about the cost implications.

13. Budget impact analysis

This budget impact analysis (BIA) describes how budgets will be affected over a five-year period if acoramidis is introduced in Denmark.

Number of patients (including assumptions of market share)

The expected number of patients eligible for treatment with acoramidis has been described in detail in Section 3.2. In this BIA, the expected number of patients eligible for treatment were estimated to be approximately 150 patients in year 1 (2025), increasing by 20 patients each year.

If acoramidis is recommended, it was assumed that acoramidis would have a market share of 10% in year 1 (2025), 20% in year 2 (2026), 30% in year 3 (2027), 40% in year 4 (2028) and 50% in year 5 (2029). It was assumed that due to the non-inferiority of acoramidis, that market share uptake will be relatively consistent and peak at 50%. Contrarily, if acoramidis is not recommended, it was assumed that tafamidis would have a market share of 100% during the entire five-year period. It is assumed that the recommendation of acoramidis does not lead to additional patients treated, i.e., it is assumed that patients treated with acoramidis would have been treated with tafamidis in a world without acoramidis.

In this BIA, a patient starting treatment with acoramidis was assumed to continue treatment with acoramidis in the following years (and the same for tafamidis). The patient numbers adjusted for market share in both scenarios (acoramidis is recommended vs. is NOT recommended) are presented in Table 47.

The price per pack (in AIP) for acoramidis and tafamidis used in the BIA was [redacted] for both treatments.

Table 47 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	2025	2026	2027	2028	2029
			Recommendation		
Acoramidis (cumulative)	15	34	57	84	115
Tafamidis (cumulative)	135	136	133	126	115
			Non-recommendation		
Acoramidis	0	0	0	0	0
Tafamidis (cumulative)	150	170	190	210	230

Budget impact

The obtained budget impact is presented in Table 48. In 2029 (year 5), the introduction of acoramidis is expected to have a budget impact of [redacted].

Table 48 Expected budget impact of recommending the medicine for the indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	110,370,478	125,086,542	139,802,605	154,518,669	169,234,733
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

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Appendix A. Main characteristics of studies included

Table 49 and Table 50 present the main characteristics of ATTRibute-CM and ATTR-ACT trials, respectively.

Table 49 Main characteristic of ATTRibute-CM

Trial name: ATTRibute-CM	**NCT number: NCT03860935**
Objective	To evaluate the efficacy and safety of acoramidis compared to placebo in patients with ATTR-CM on stable HF therapy (61)
Publications – title, author, journal, year	Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. New England Journal of Medicine. 2024;390(2):132-142. doi:10.1056/NEJMoa2305434 Judge DP, Gillmore JD, Alexander KM, Ambardekar AV, Cappelli F, Fontana M, García-Pavía P, Grodin JL, Grogan M, Hanna M, Masri A, Nativi-Nicolau J, Obici L, Hvitfeldt Poulsen S, Sarswat N, Shah K, Soman P, Lystig T, Cao X, Wang K, Pecoraro ML, Tamby JF, Katz L, Sinha U, Fox JC, Maurer MS. Long-Term Efficacy and Safety of Acoramidis in ATTR-CM: Initial Report From the Open-Label Extension of the ATTRibute-CM Trial. Circulation. 2024 Nov 18. doi: 10.1161/CIRCULATIONAHA.124.072771.
Study type and design	ATTRibute-CM was a phase 3 randomized, double-blinded, placebo-controlled study for 30 months in adult patients (aged ≥18 to ≤90 years) with symptomatic ATTR-CM and on stable HF therapy (61). Patients were also stratified at randomization based on TTR genotype (wild-type vs. variant), NT-proBNP levels, and eGFR (61). Efficacy and safety outcome assessments were performed on Day 1, Day 28, Month 3, and repeated every 3 months until Month 30 (61). Additionally, there were monthly telephone sessions to assess safety (61).
Sample size (n)	ITT population: 632 patients (Acoramidis n=421, Placebo n=211) mITT population: 611 patients (Acoramidis n=409, Placebo n=202)
Main inclusion criteria	• Adults aged ≥18 to ≤90 years • Established diagnosis of ATTR-CM based on endomyocardial biopsy with confirmed typing or positive results on technetium-99m scintigraphy, and biochemical exclusion of light chain amyloidosis • NYHA Class I to III symptoms due to ATTR-CM • Clinical HF with ≥1 previous hospitalization for HF or signs of volume overload, or HF requiring diuretic treatment

Trial name: ATTRibute-CM	NCT number: NCT03860935
	• 6MWT ≥150 metres • NT-proBNP ≥300 pg/mL • LV wall thickness ≥13 mm
Main exclusion criteria	• Acute coronary syndrome, coronary revascularization, stroke, or transient ischemic attack in the 90 days prior to screening • Likely to receive a heart transplant within a year after screening • Current treatment with marketed drug products or other investigational agents for ATTR-CM • Abnormal liver function tests (ALT, AST >2 times ULN or total bilirubin >3 times ULN) • NT-proBNP ≥8,500 pg/mL • EGFR <15 ML/MIN/1.73 m^2
Intervention	Acoramidis 800 mg twice daily (n=421)
Comparator(s)	Matching placebo (n=211)
Follow-up time	The follow-up coincided with the treatment period: Part A: 0–12 months Part B: 12–30 months with tafamidis allowed as a concomitant medication
Is the study used in the health economic model?	No. This study was included in this application to demonstrate acoramidis has similar efficacy and safety to tafamidis. In this application, only a CMA was submitted.
Primary, secondary and exploratory endpoints	Primary efficacy endpoints: Part A: CFB in 6MWT to month 12 of treatment Part B: Hierarchical combination of ACM and cumulative frequency of CV-related hospitalizations, CFB in the NT-proBNP, and CFB in 6MWT over a 30-month period Secondary efficacy endpoints: Part A: CFB in KCCQ-OS/TTR level/TTR stabilization to month 12 of treatment and safety Part B: CFB in 6MWT/KCCQ-OS/TTR level/TTR stabilization to month 30 of treatment A hierarchical combination of ACM and CV-related hospitalization over a 30-month period

Trial name: ATTRibute-CM	NCT number: NCT03860935
	ACM, CV-related mortality, cumulative frequency of CV-related hospitalization by month 30, and safety Exploratory endpoints for Parts A and B: CFB in NT-proBNP/Troponin I/EQ-5D-5L, PK-PD analyses, and additional assays comparing acoramidis activity across a panel of TTR variants Safety (secondary endpoints): Treatment-emergent serious adverse events (TESAEs) and adverse events (AEs), AEs leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern. **Endpoints included in this application:** Efficacy endpoints: The individual components of the primary efficacy endpoint (i.e, ACM and cumulative frequency of CV-related hospitalizations, CFB in the NT-proBNP, and CFB in 6MWT over a 30-month period). All were secondary efficacy endpoints, with the exception of CFB in the NT-proBNP which was an exploratory endpoint. Safety endpoints: TEAEs and TESAEs were included. HRQoL: CFB in KCCQ-OS (secondary outcome). **Other endpoints:** Results are not included in this application for the remaining endpoints.
Method of analysis	**Efficacy** All efficacy analyses were conducted on the modified intention-to-treat population. This was the primary analysis population for efficacy endpoints and included participants who met the definition of ITT and had a baseline eGFR ≥ 30 mL/min/1.73 m^2. Primary endpoint The primary efficacy analysis used the F-S test in which each participant was compared to every other participant within each stratum in a pair-wise manner. The analytical stepwise approach prioritized all-cause mortality as the first hierarchical step, followed by the frequency of CV-related hospitalization as the second step, clinically meaningful difference (≥ 500 pg/mL) in change from baseline in NT-proBNP as the third step, and the difference in change from baseline in 6MWD as the fourth and final step. In this stepwise approach, a subsequent step was considered in the hierarchy only when the participant pair being considered could not be differentiated on the basis of the variable in the prior step. The win ratios were calculated to provide a point estimate and corresponding confidence interval (CI) of the treatment difference and complement the results of the primary efficacy analysis from the F-S scoring algorithm (which generates a p value but not a point estimate). The stratified non-matched win ratio method

Trial name: ATTRibute-CM	NCT number: NCT03860935

compares all participants in the treated group with those in the placebo group within each stratum in pairs under the same hierarchical structure of the F-S test. The win ratios were calculated by adding all wins from the treatment group and dividing it by all wins from the placebo group within each hierarchical step in the analysis.

No missing data were imputed for the primary analysis.

Secondary endpoints

To maintain the αB for the key secondary endpoints, the key secondary endpoints were formally tested per the multiplicity adjustment rule.

6MWT: The key secondary efficacy endpoint of change from baseline in distance walked during the 6MWT for the imputed datasets was analyzed using a MMRM with an unstructured covariance matrix.

KCCQ-OS: Same analytical approach to 6MWT

ACM: The time to All-Cause Mortality was analyzed using a stratified Cox proportional hazards model that includes treatment as an explanatory factor along with baseline 6MWT. P-values and confidence intervals for the HR were based on the Wald statistic.

CV-related hospitalization: Cumulative frequency of CEC adjudicated CV-related hospitalization will be analyzed using negative binomial regression analysis with treatment, the three stratification factors and an offset term equal to log of each subject’s study duration included in the model. If the number of subjects with zero CV-related hospitalization is high, a zero inflated negative binomial model will be performed to provide further assurance of the results. Stratified Cochran-Mantel-Haenszel (CMH) row means scores tests will be used to analyze the frequency of CEC adjudicated cardiovascular-related hospitalizations by treatment.

NT-proBNP: Same analytical approach to 6MWT

Safety

The analysis set for safety analyses was the safety analysis population: all participants dosed.

Safety parameters assessed included treatment-emergent adverse events (TEAEs) and serious TEAEs (including CV events reported by the Investigator as TEAEs/SAEs), TEAEs leading to study drug discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of clinical relevance. Analysis by eGFR group (≥ 30 versus < 30 mL/min/1.73 m^2) at Screening was conducted for summaries of TEAEs, clinical laboratory parameters, liver function tests, vital signs, and ECG.

Trial name: ATTRibute-CM	**NCT number: NCT03860935**
Subgroup analyses	Pre-specified analyses were conducted to explore efficacy within the subgroups based on age, wild-type versus variant, baseline NT-proBNP, country of enrollment, baseline renal function, and NYHA Class.
Other relevant information	N/A.

Abbreviations: 6MWT, 6-minute walk test; ACM, All-cause mortality; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, Change form baseline; CMA, Cost-minimization analysis; CV, Cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; LV, left ventricular; N/A, Not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ULN, upper limit of normal
Source: (46, 47).

Table 50 Main characteristic of ATTR-ACT

Trial name: ATTR-ACT	**NCT number: NCT01994889**
Objective	To determine the efficacy, safety and tolerability of tafamidis meglumine in comparison to placebo in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy.
Publications – title, author, journal, year	Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Circ Heart Fail. 2017 Jun;10(6):e003815. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-1016. Extrapolation of survival benefits in patients with transthyretin amyloid cardiomyopathy receiving tafamidis: analysis of the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. Li B, Alvir J, Stewart M. Cardiol Ther. 9:535-540. 2020. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R Eur J Heart Fail. 23(2):277-285. 2021. Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS .. Am] Cardiol. 141:98-105. 2021. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, Boman K, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS. JACC Heart Fail. 9(2):115-123. 2021.

Trial name: ATTR-ACT	**NCT number: NCT01994889**
	Causes of cardiovascular hospitalization and death in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial [ATTR-ACT]). Miller AB, Januzzi JL, O'Neill BJ, Gundapaneni B, Patterson TA, Sultan MB, Lopez-Sendon J. Am J Cardiol. 148:146-150. 2021. Modeling of Survival and Frequency of Cardiovascular-Related Hospitalization in Patients with Transthyretin Amyloid Cardiomyopathy Treated with Tafamidis. Vong, C., Boucher, M., Riley, S., Harnisch LO. Am J Cardiovasc Drugs, 21:535-543. 2021 Health impact of tafamidis in transthyretin amyloid cardiomyopathy patients: an analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the open-label long-term extension studies. Rozenbaum MH, Garcia A, Grima D, Tran D, Bhambri R, Stewart M, Li B, Heeg B, Postma M, Masri A. Eur Heart J Qual Care Clin Outcomes. 8:529-538 2021. Natural history and progression of transthyretin amyloid cardiomyopathy: insights from (ATTR-ACT). Nativi-Nicolau J, Judge DP, Hoffman JE, Gundapaneni B, Keohane D, Sultan MB, Grogan M. ESC Heart Failure. 8:3875-3884. 2021. Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). Rozenbaum MH, Large S, Bhambri R, Stewart M, Young R, van Doornewaard A, Dasgupta N, Masri A, Nativi-Nicolau J. J Compar Effect Res. 10(11):927-938. 2021. Estimating the Effect of Tafamidis on Cardiovascular-Related Hospitalization in NYHA Class III Patients with Transthyretin Amyloid Cardiomyopathy in the Presence of Death. Li H, Rozenbaum M, Casey M, Sultan MB. Cardiology. 147(4):398-405. 2022. Relationship of binding-site occupancy, transthyretin stabilisation and disease modification in patients with tafamidis-treated transthyretin amyloid cardiomyopathy. Tess DA, Maurer TS, Li Z, Bulawa C, Fleming J, Moody AT. Amyloid.30(2):208-219. 2023. Improvements in efficacy measures with tafamidis in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). Hanna M, Fine N, Gundapaneni B, Sultan M. Witteles R. JACC: Advances. 1(5):1-8.2022. Annual cardiovascular-related hospitalization days avoided with tafamidis in patients with transthyretin amyloid cardiomyopathy. Rozenbaum M, Tran D, Bhambri R, Nativi-Nicolau J. Am J Cardiovasc Drugs. 22(4):445-450. 2022. Association of Tafamidis With Health Status in Patients With ATTR

Trial name: ATTR-ACT	NCT number: NCT01994889
	Cardiac Amyloidosis: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. Sperry BW, Hanna M, Maurer MS, Nativi-Nicolau J, Floden L, Stewart M, Wyrwich KW, Barsdorf AI, Kapadia H, Spertus JA. JAMA Cardiol. 8(3):275-280. 2023. Tafamidis and quality of life in people with transthyretin amyloid cardiomyopathy in the study ATTR-ACT: A plain language summary. Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Sultan MB, Maurer MS. Future Cardiol. 18(3):165-172. 2022. Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study. Garcia-Pavia P, Sultan MB, Gundapaneni B, Sekijima Y, Perfetto F, Hanna M, Witteles R. JACC: Heart Failure. 12(1):150-160. 2023. Effect of Tafamidis on Cardiac Function in Patients With Transthyretin Amyloid Cardiomyopathy: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. Shah S, Fine N, Garcia-Pavia P, Klein A, Fernandes F, Weissman N, Maurer M, Boman K, Gundapaneni B, Sultan MB, Elliott P. JAMA Cardiol. 9(1):25-34. 2023.
Study type and design	Phase 3, international, multicentre, placebo-controlled, double-blind, parallel-group design, randomized clinical trial. Patients were randomly assigned to receive 80 mg of tafamidis meglumine, 20 mg of tafamidis meglumine, or matching placebo once daily in a ratio of 2:1:2. Stratification was conducted according to TTR genotype (variant or wild-type) and baseline disease severity determined by New York Heart Association class (NYHA class I and II combined or NYHA class III). Enrolment started December 2013 and study was completed February 2018.
Sample size (n)	632 patients (Acoramidis n=421, Placebo n=211)
Main inclusion criteria	1. Men and women aged 18-90 years 2. Medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral oedema) that required/requires treatment with a diuretic for improvement 3. Documented TTR amyloid cardiomyopathy in accordance with institutional site standard of care, which is defined as: a. Hereditary TTR amyloid cardiomyopathy defined by all of the following: • Presence of a variant TTR genotype associated with cardiomyopathy phenotype (e.g. a history of congestive heart failure),

Trial name: ATTR-ACT	**NCT number: NCT01994889**
	1) TTR genotyping is required at screening unless documentation of a prior determination of a TTR genotype is produced, 2) Subjects with a confirmed diagnosis of hereditary (variant genotype) ATTR-CM with concurrent monoclonal gammopathy of undetermined significance (MGUS) based on serum or urine light chain determinations, should be tested in the same manner as in the case of equivocal immunohistochemistry for subjects with wild-type ATTR-CM below, • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm • Presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or Alcian blue stain). b. Wild-type TTR amyloid cardiomyopathy defined by all of the following: • Absence of variant genotype • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm • Presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or Alcian blue stain). • TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry 4. NT-proBNP concentration ≥ 600 pg/ml 5. 6-minute walk test (6MWT) distance > 100 m
Main exclusion criteria	1. Presence of primary (light chain) amyloidosis 2. Prior liver or heart transplantation, or implanted cardiac mechanical assist device 3. New York Heart Association (NYHA) classification IV 4. Modified body mass index (mBMI) < 600 kg/m^2 ·g/L 5. Taking or have previously taken tafamidis 6. Requiring treatment with calcium channel blockers or digitalis 7. Renal failure requiring dialysis and/or have an estimated glomerular filtration rate (eGRF) of < 25 mL/min/1.73 m^2

Trial name: ATTR-ACT	NCT number: NCT01994889
	8. History of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed 9. Heart failure that in the opinion of the investigator is based on ischemic heart disease, or uncorrected valvular disease and not primarily due to transthyretin amyloid cardiomyopathy 10. Drugs not allowed according to protocol
Intervention	Tafamidis meglumine 80 mg or 20 mg, both administered in soft gel capsules once daily for 30 months. 264 patients were randomized to the pooled group that received tafamidis meglumine treatment (80 mg n=176; 20 mg n=88).
Comparator(s)	177 patients were randomized to the placebo group that received matching placebo capsules.
Follow-up time	The trial duration was 30 months (completed). On completion patients were offered enrolment in an extension study (Protocol B3461045, NCT02791230), the extension study is ongoing.
Is the study used in the health economic model?	No. This study was included in this application to demonstrate acoramidis has similar efficacy and safety to tafamidis. In this application, only a CMA was submitted.
Primary, secondary and exploratory endpoints	Primary endpoint: Hierarchical combination of 1. all-cause mortality and 2. frequency of cardiovascular-related hospitalizations (defined as a nonelective admission to an acute care setting for medical therapy for cardiovascular-related morbidity resulting in at least a 24-hour stay) Key secondary endpoints 1. Change from baseline to month 30 in distance walked on the 6-minute walk test (6MWT), a measure of functional capacity 2. Change from baseline to month 30 in the Kansas City Cardiomyopathy Questionnaire - Overall Summary (KCCQ-OS) score, which assesses quality of life Secondary endpoints 1. All-cause mortality 2. Frequency of cardiovascular-related hospitalization 3. Cardiovascular-related mortality (not published yet) 4. TTR stabilization at month 1

Trial name: ATTR-ACT	NCT number: NCT01994889
	Endpoints included in this application: Efficacy endpoints: ACM and cumulative frequency of CV-related hospitalizations, CFB in the NT-proBNP, and CFB in 6MWT over a 30-month period. Safety endpoints: TEAEs and TESAEs. HRQoL: CFB in KCCQ-OS. **Other endpoints:** Results are not included in this application for the remaining endpoints.
Method of analysis	The analyses were carried out on the intent-to-treat (ITT) population, which included all patients who were enrolled, received at least 1 dose of tafamidis or placebo, and had at least 1 after-baseline efficacy evaluation. Changes in EQ-SD-3L Index Score and EQ-VAS at each time point were prespecified exploratory end points. Continuous variables were analyzed using a mixed model, repeated measures analysis of covariance with an unstructured covariance matrix; center and patient within center as random effects; treatment, visit, TTR genotype [vATTR and wtATTR), and visit by treatment interaction as fixed effects; and baseline score as covariate. There was no imputation of missing values. The patients in the tafamidis 80 mg and tafamidis 20 mg groups were pooled to form a single pooled tafamidis group which was compared to placebo in all analyses. The primary analysis hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations with the use of the Finkelstein– Schoenfeld method, which is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. This method gives a higher importance to all-cause mortality. The Finkelstein-Schoenfeld method was discussed and agreed with authorities before initiation of the study. For subjects who discontinued before month 30, a vital status follow-up was conducted at month 30 to obtain their mortality status for use in the analysis. Heart transplantation, combined heart and liver transplantation, and implantation of a cardiac mechanical assist device were treated as death for the purposes of this analysis. All cause-mortality was analyzed with the use of Cox proportional-hazards model, with treatment and the stratification factors treated as covariates. Patients who discontinued for transplantation (i.e. heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the same manner as death.

Trial name: ATTR-ACT	NCT number: NCT01994889
	Frequency of cardiovascular-related hospitalizations were compared with the use of a Poisson regression model, with treatment, TTR genotype, (variant and wild-type), NYHA baseline class (NYHA class I and II combined vs NYHA class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treatment duration. The key secondary endpoints were assessed with the use of a mixed-effect model, repeated-measure approach and analysis of covariance, with an unstructured covariance matrix. Centre and patient-within-centre were treated as random effects, and treatment, visit, TTR genotype (vATTR vs wtATTR), and visit-by-treatment interaction were treated as fixed effects, with the baseline value as covariate. A prespecified hierarchical testing order (6MWT, followed by the KCCQ-OS) provided multiplicity protection against type 1 error. The remaining secondary and exploratory analyses and endpoints were not adjusted for multiplicity. All analyses were pre-specified in the protocol.
Subgroup analyses	None
Other relevant information	None

Source: (3, 43)

Appendix B. Efficacy results per study

Results per study

Table 51 and Table 52 present the study results for the ATTRibute-CM and ATTR-ACT trials, respectively.

ATTRibute-CM

Table 51 Results per study – ATTRibute-CM

Results of ATTRibute-CM Trial (NCT03860935)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Pair-wise win ratio for hierarchical combinations	Acoramidis	409	Total wins: 18,346 (NA)	NA	NA	NA	1.772	96%CI: 1.402-2.240	NA	The win ratios were determined by an F-S scoring algorithm of hierarchical combination of all-cause mortality, frequency of CV-related hospitalizations, difference in change from baseline in NT-proBNP and in change from baseline in 6MWD for 30 months.	(46)
	Placebo	202	Total wins: 10,351 (NA)								(46)

Results of ATTRibute-CM Trial (NCT03860935)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in 6MWD at month 30	Acoramidis	384	-64.65 (-75.45 to -53.86)	39.64	21.07-58.22	<0.0001	NA	NA	NA	The change from baseline in 6MWD at month 30 is calculated using MMRM and reported as difference in least squares means	(46)
	Placebo	186	-104.29 (-119.53 to -89.06)								(46)
Change from baseline in KCCQ-OS at month 30	Acoramidis	405	−11.48 (-13.79 to -9.16)	9.94	5.97, 13.91	<0.0001	NA	NA	NA	The absolute difference in effect is estimated using MMRM with a modified intent-to-treat population and reported by least squares mean.	(46)
	Placebo	201	−21.42 (-24.66 to -18.18)								(46)
Change from baseline in TTR level (mg/dL) at month 30	Acoramidis	397	5.78 (5.1-6.54)	7.10	5.79-8.40	<0.0001	NA	NA	NA	The absolute difference in effect is estimated using least squares mean differences with a modified intent-to-treat population by using MMRM.	(46)
	Placebo	197	-1.32 (-2.38 to -0.26)								(46)
	Acoramidis	409	19.3% (NA)	NA	NA	NA	HR: 0.772	0.542-1.102	0.1543		(46)

Results of ATTRibute-CM Trial (NCT03860935)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
All-cause mortality	Placebo	202	25.7% (NA)							The HR is based on a stratified Cox proportional hazards model with treatment as an explanatory factor and baseline 6MWD as covariate	(46)
All-cause mortality	Acoramidis	409	19.3% (NA)	NA	NA	NA	HR: 0.774	0.543-1.104	0.1577	The HR is based on the stratified Cox proportional model with the addition of a time covariate for introduction of tafamidis.	(46)
	Placebo	202	25.7% (NA)								(46)
Frequency of CV-related hospitalizations per year	Acoramidis	409	0.224 (0.180-0.277)	NA	NA	NA	RR: 0.496	0.355-0.695	<0.0001	The relative risk ratio on the annualized frequency of CV-related hospitalizations were estimated using a negative binomial regression analysis. Imputation of missing data were added.	(46)
	Placebo	202	0.450 (0.347-0.584)								(46)
AGM fold-change	Acoramidis	397	1.465 (1.356-1.583)	NA	NA	NA	0.529	0.463-0.604	<0.0001	The estimated relative difference in effect of change	(46)

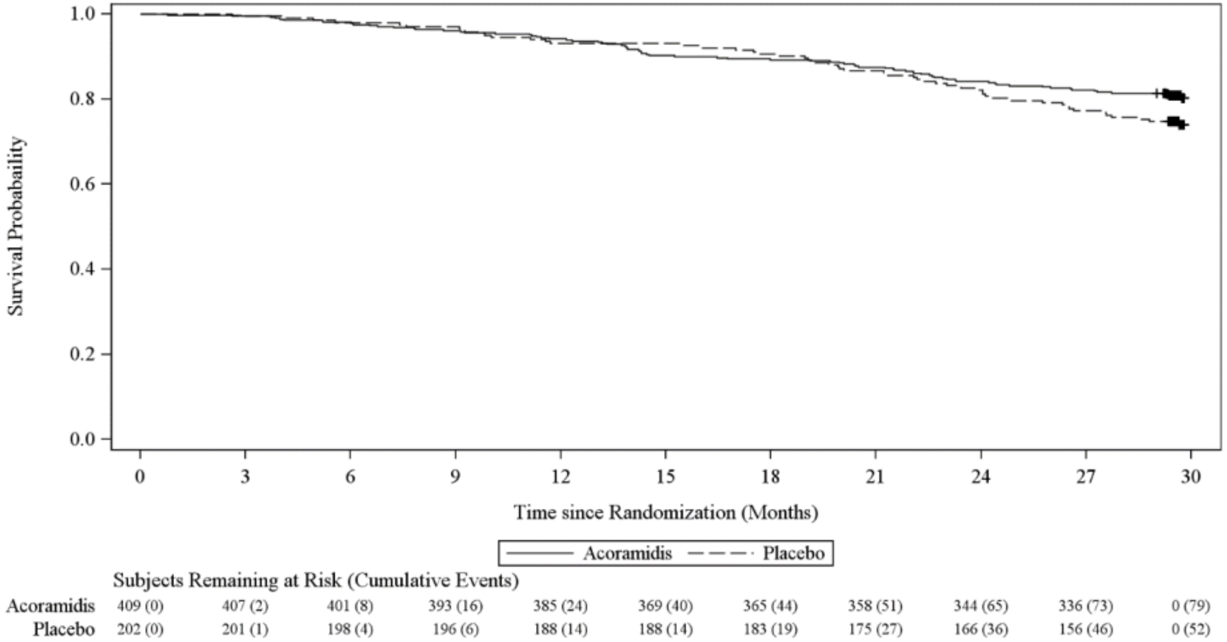
Results of ATTRibute-CM Trial (NCT03860935)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
from baseline in NT-proBNP (pg/mL) at month 30	Placebo	198	2.771 (2.485 to 3.091)							from baseline in NT-proBNP were found using the AGM mean fold change based on the MMRM.	(46)
Change from baseline in EQ-5D-5L VAS at month 30	Acoramidis	402	-10.12 (-12.49 to -7.74)	9.55	5.50-13.59	<0.0001	NA	NA	NA	The difference in effect from baseline in EQ-5D-5L VAS were computed using least squares mean for the two treatment groups.	(46)
	Placebo	200	-19,66 (-22.95 to -16.37)								(46)

Abbreviations: 6MWT: 6-minute walk test; ANCOVA, Analysis of Covariance; CI, confidence interval; F-S, Finkelstein-Schoenfeld; 6MWD, 6-minute walk distance; MMRM, Mixed Models for Repeated Measures; CV, cardiovascular; proBNP, N-terminal prohormone of brain natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; TTR, transthyretin; AGM, Adjusted Geometric Mean; EQ-5D-5L, EuroQol 5-dimensions 5-levels Health Outcomes Assessment; VAS, visual analog scale.

Additional results for ACM (ATTRibute-CM)

Kaplan-Meier curves for time to all-cause mortality, including heart transplant and CMAD, are shown in Figure 7. The curves were observed to cross multiple times early in the study before their eventual separation starting at 19 months.

Figure 7 Kaplan-Meier Curve for Time to All-cause Mortality Over Month 30, mITT Population



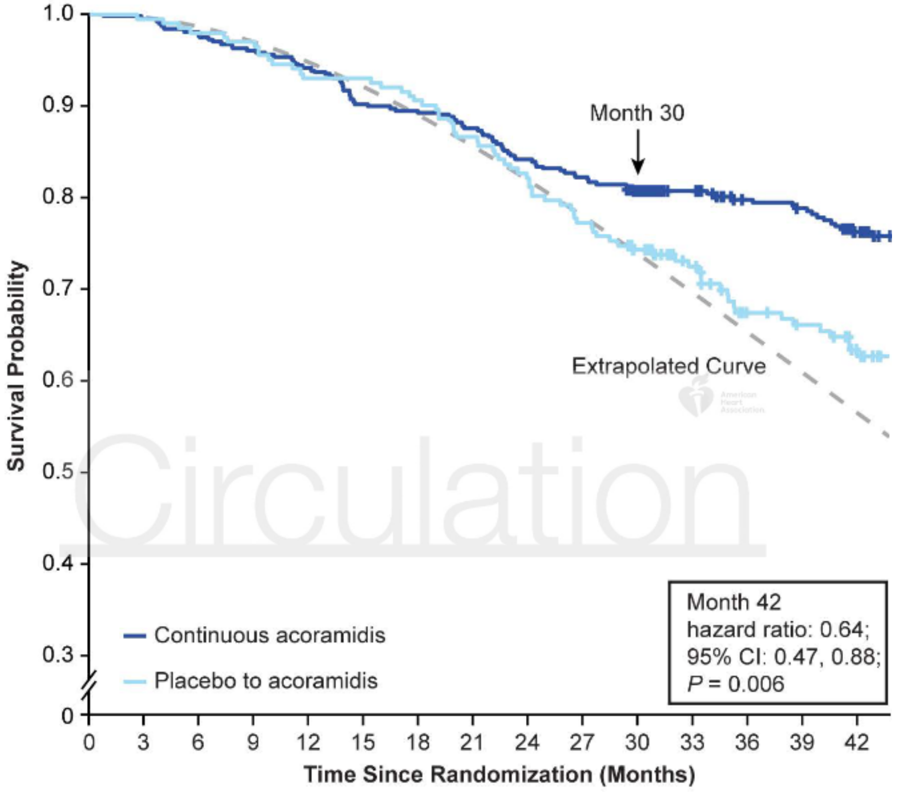
Subjects Remaining at Risk (Cumulative Events)

	0	3	6	9	12	15	18	21	24	27	30
Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

Abbreviations: CMAD, cardiac mechanical assist device; mITT, modified intent-to-treat
Note: All-cause mortality included heart transplant, CMAD and all-cause death
Source: (46).

In a recently published study reporting on open-label extension data for acoramidis, Judge et al. observed that there may be a trend of reduction in the risk of ACM in this arm following initiation of acoramidis in the OLE as observed out to Month 42 (Figure 8). While the trajectory of events accruing over time in the placebo to acoramidis group appears to persist from Month 30, additional follow-up in this ongoing study may clarify the currently observed favorable impact of acoramidis treatment in this group (68).

Figure 8 Kaplan–Meier Curve for Time to All-Cause Mortality from Baseline in ATTRibute-CM study through Month 42 in the OLE study



Participants Remaining at Risk (Cumulative Events)

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Continuous acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	297 (79)	260 (79)	247 (82)	243 (85)	216 (93)
Placebo to acoramidis	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	143 (52)	118 (55)	102 (63)	98 (65)	87 (70)

Data are for the full analysis set. The full analysis set included the modified intention-to-treat population in ATTRibute-CM, which was defined as all participants who were randomized to acoramidis or placebo, received ≥ 1 dose of acoramidis or placebo, had ≥ 1 efficacy evaluation after baseline, and had baseline eGFR of ≥ 30 mL/min/1.73 m^2. The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study. Data were analyzed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomization stratification factors of genotype, NT-proBNP, and eGFR. The extrapolated curve shows expected results if participants had continued receiving placebo in the OLE study. Survival probabilities for placebo to acoramidis treatment group beyond Month 30, assuming no open-label acoramidis had been taken, were extrapolated based on a Weibull probability model for the time to the ACM event estimated from the data observed in the ATTRibute-CM study and represented by the dotted line. Abbreviations: 6MWD, 6-minute walk distance; ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OLE, open-label extension.
Source: (68).

ATTR-ACT

Table 52 Results per study – ATTR-ACT

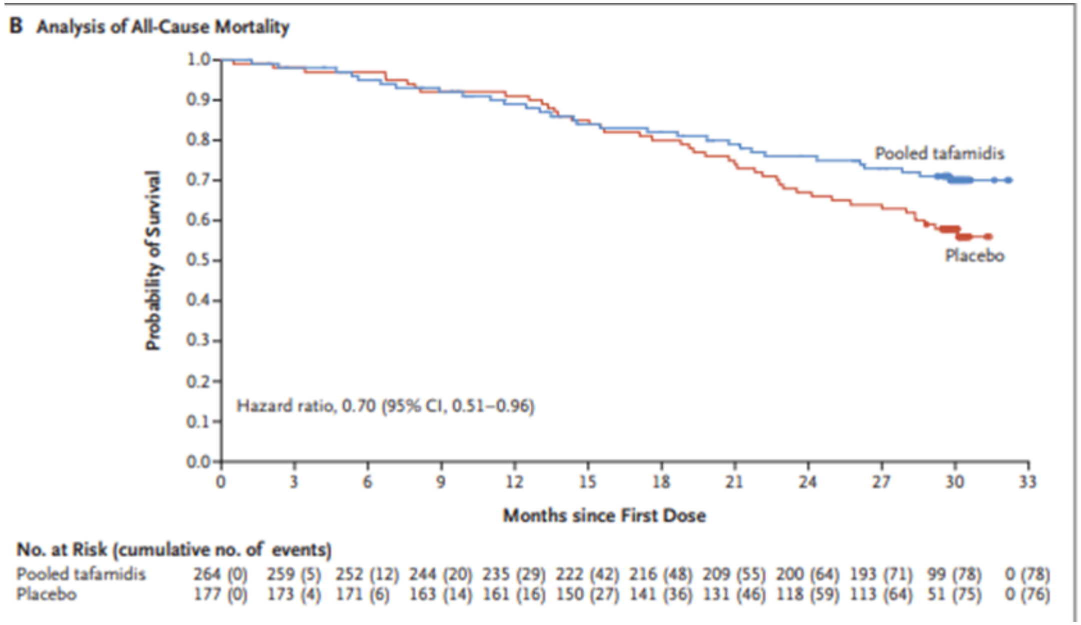
Results of ATTR-ACT (NCT01994889)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
All-cause mortality	Tafamidis 80 mg	176	30.7% (NA)	15 990	NA	NA	HR: 0.690	0.487-0.979	0.0378	The all-cause mortality was estimated by the Cox proportional hazards model.	(44, 58, 60)
	Placebo	177	42.9% (NA)								(44, 58, 60)
Frequency of CV-related hospitalizations	Tafamidis 80 mg	176	0.49 (NA)	NA	NA	NA	RR: 0.70	0.57-0.85	0.0005	The relative risk ratio in frequency of CV-related hospitalizations was estimated through a Poisson regression.	(44, 58, 60)
	Placebo	177	0.70 (NA)								(44, 58, 60)

Results of ATTR-ACT (NCT01994889)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change from baseline at month 30 in NT-proBNP	Tafamidis 80 mg	110	1371.71 (NA)	-2587.54	NA	<0.0001	NA	NA	NA	The absolute difference in effect is estimated using least squares mean differences.	(44, 58, 60)
	Placebo	80	3959.25 (NA)								(44, 58, 60)
Change from baseline at month 30 in 6MWT	Tafamidis 80 mg	176	NA	75.77	NA	<0.0001	NA	NA	NA	The difference in effect from baseline at month 30 in 6MWT was evaluated using a MMRM ANCOVA and reported as the difference in least squares mean.	(44, 58, 60)
	Placebo	177	NA								(44, 58, 60)
Change from baseline at month 30 in KCCQ-OS	Tafamidis 80 mg	176	NA	13.48	NA	<0.0001	NA	NA	NA	The difference in effect was evaluated by a MMRM ANCOVA and measured by the difference in least squares mean at month 30.	(44, 58, 60)
	Placebo	177	NA								(44, 58, 60)

6MWT: 6-minute walk test; ANCOVA, Analysis of Covariance; CI, confidence interval; 6MWD, 6-minute walk distance; MMRM, Mixed Models for Repeated Measures; NA, Not available; CV, cardiovascular; proBNP, N-terminal prohormone of brain natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

Additional results for ACM (ATTR-ACT)

Figure 9 Analysis of all-cause mortality



No. at Risk (cumulative no. of events)

	0	3	6	9	12	15	18	21	24	27	30	33
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

Source: (51).

Appendix C. Comparative analysis of efficacy

A meta-analyses was not conducted hence Table 53 was not used. See Section C.1 below for a description of the methodology and the results from the matching-adjusted indirect comparison conducted for the comparative analyses of efficacy and safety.

Table 53 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Not Applicable									

C.1 Matching-adjusted indirect comparison

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Appendix D. Extrapolation

Not applicable as the CMA model does not include (nor extrapolates) efficacy measures. The following headings in this appendix are not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

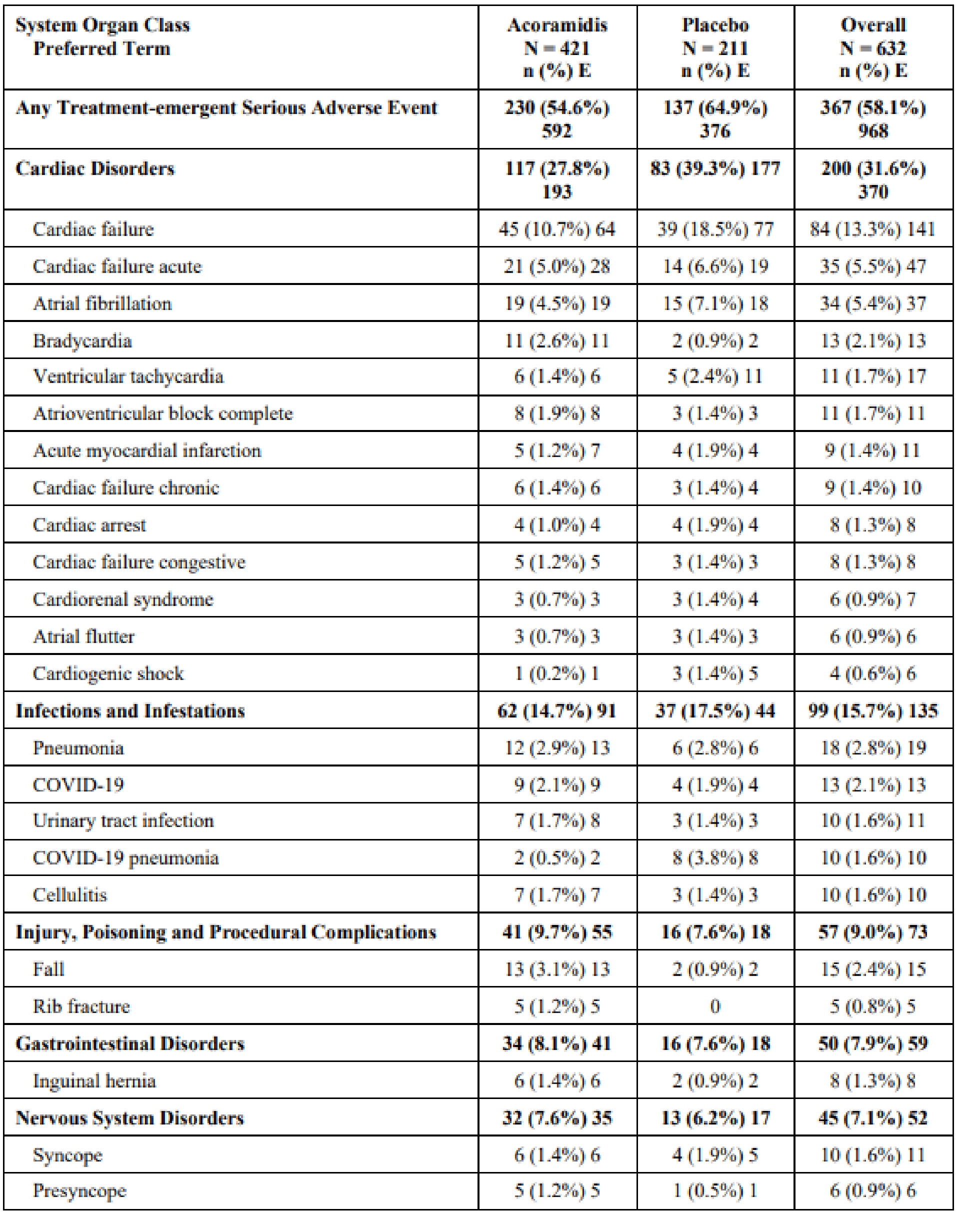
Not applicable.

Appendix E. Serious adverse events

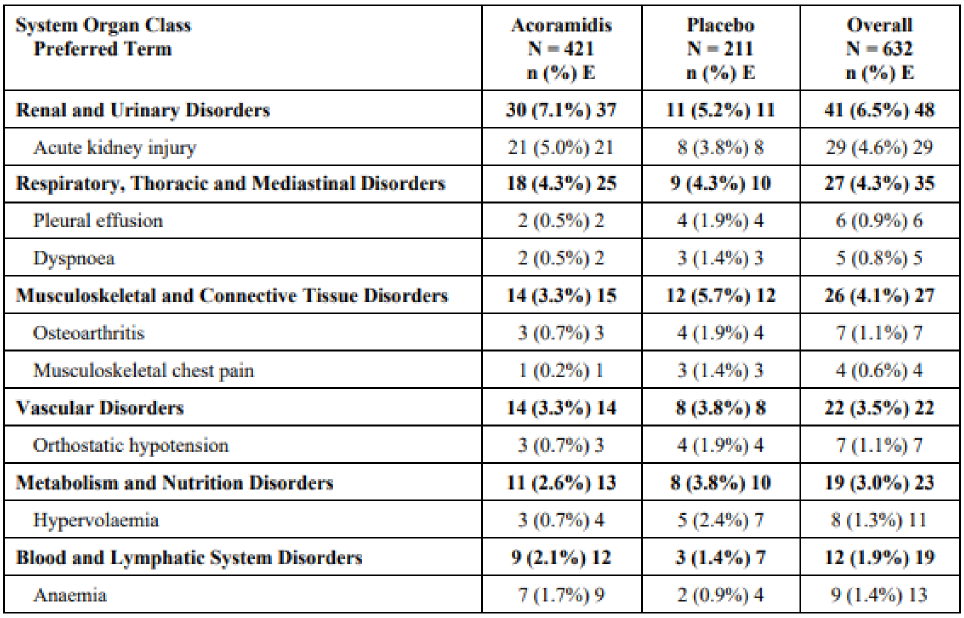
E.1 ATTRibute-CM data on serious adverse events

Table 56 presents the serious adverse events registered for participants who received acoramidis until month 30 (46).

Table 56 Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Reported in >1% of Participants for any PT in Either Treatment Group, Safety Population



System Organ Class Preferred Term	Acoramidis N = 421 n (%) E	Placebo N = 211 n (%) E	Overall N = 632 n (%) E
Any Treatment-emergent Serious Adverse Event	**230 (54.6%) 592**	**137 (64.9%) 376**	**367 (58.1%) 968**
Cardiac Disorders	**117 (27.8%) 193**	**83 (39.3%) 177**	**200 (31.6%) 370**
Cardiac failure	45 (10.7%) 64	39 (18.5%) 77	84 (13.3%) 141
Cardiac failure acute	21 (5.0%) 28	14 (6.6%) 19	35 (5.5%) 47
Atrial fibrillation	19 (4.5%) 19	15 (7.1%) 18	34 (5.4%) 37
Bradycardia	11 (2.6%) 11	2 (0.9%) 2	13 (2.1%) 13
Ventricular tachycardia	6 (1.4%) 6	5 (2.4%) 11	11 (1.7%) 17
Atrioventricular block complete	8 (1.9%) 8	3 (1.4%) 3	11 (1.7%) 11
Acute myocardial infarction	5 (1.2%) 7	4 (1.9%) 4	9 (1.4%) 11
Cardiac failure chronic	6 (1.4%) 6	3 (1.4%) 4	9 (1.4%) 10
Cardiac arrest	4 (1.0%) 4	4 (1.9%) 4	8 (1.3%) 8
Cardiac failure congestive	5 (1.2%) 5	3 (1.4%) 3	8 (1.3%) 8
Cardiorenal syndrome	3 (0.7%) 3	3 (1.4%) 4	6 (0.9%) 7
Atrial flutter	3 (0.7%) 3	3 (1.4%) 3	6 (0.9%) 6
Cardiogenic shock	1 (0.2%) 1	3 (1.4%) 5	4 (0.6%) 6
Infections and Infestations	**62 (14.7%) 91**	**37 (17.5%) 44**	**99 (15.7%) 135**
Pneumonia	12 (2.9%) 13	6 (2.8%) 6	18 (2.8%) 19
COVID-19	9 (2.1%) 9	4 (1.9%) 4	13 (2.1%) 13
Urinary tract infection	7 (1.7%) 8	3 (1.4%) 3	10 (1.6%) 11
COVID-19 pneumonia	2 (0.5%) 2	8 (3.8%) 8	10 (1.6%) 10
Cellulitis	7 (1.7%) 7	3 (1.4%) 3	10 (1.6%) 10
Injury, Poisoning and Procedural Complications	**41 (9.7%) 55**	**16 (7.6%) 18**	**57 (9.0%) 73**
Fall	13 (3.1%) 13	2 (0.9%) 2	15 (2.4%) 15
Rib fracture	5 (1.2%) 5	0	5 (0.8%) 5
Gastrointestinal Disorders	**34 (8.1%) 41**	**16 (7.6%) 18**	**50 (7.9%) 59**
Inguinal hernia	6 (1.4%) 6	2 (0.9%) 2	8 (1.3%) 8
Nervous System Disorders	**32 (7.6%) 35**	**13 (6.2%) 17**	**45 (7.1%) 52**
Syncope	6 (1.4%) 6	4 (1.9%) 5	10 (1.6%) 11
Presyncope	5 (1.2%) 5	1 (0.5%) 1	6 (0.9%) 6



System Organ Class Preferred Term	Acoramidis N = 421 n (%) E	Placebo N = 211 n (%) E	Overall N = 632 n (%) E
Renal and Urinary Disorders	**30 (7.1%) 37**	**11 (5.2%) 11**	**41 (6.5%) 48**
Acute kidney injury	21 (5.0%) 21	8 (3.8%) 8	29 (4.6%) 29
Respiratory, Thoracic and Mediastinal Disorders	**18 (4.3%) 25**	**9 (4.3%) 10**	**27 (4.3%) 35**
Pleural effusion	2 (0.5%) 2	4 (1.9%) 4	6 (0.9%) 6
Dyspnoea	2 (0.5%) 2	3 (1.4%) 3	5 (0.8%) 5
Musculoskeletal and Connective Tissue Disorders	**14 (3.3%) 15**	**12 (5.7%) 12**	**26 (4.1%) 27**
Osteoarthritis	3 (0.7%) 3	4 (1.9%) 4	7 (1.1%) 7
Musculoskeletal chest pain	1 (0.2%) 1	3 (1.4%) 3	4 (0.6%) 4
Vascular Disorders	**14 (3.3%) 14**	**8 (3.8%) 8**	**22 (3.5%) 22**
Orthostatic hypotension	3 (0.7%) 3	4 (1.9%) 4	7 (1.1%) 7
Metabolism and Nutrition Disorders	**11 (2.6%) 13**	**8 (3.8%) 10**	**19 (3.0%) 23**
Hypervolaemia	3 (0.7%) 4	5 (2.4%) 7	8 (1.3%) 11
Blood and Lymphatic System Disorders	**9 (2.1%) 12**	**3 (1.4%) 7**	**12 (1.9%) 19**
Anaemia	7 (1.7%) 9	2 (0.9%) 4	9 (1.4%) 13

Abbreviations: COVID-19, coronavirus disease 2019; n, number of participants experiencing a treatment-emergent serious adverse event (the participant was counted only once for each SAE); N, total number of participants in the study arm; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event % is of the column total. E is the number of events for system organ class or preferred term. An SAE that occurred more than 30 days after the last dose of study drug was not counted as a TEAE. System organ class and preferred term coded using MedDRA Version 24.1.

Source: (46).

E.2 ATTR-ACT data on serious adverse events

No further data is publicly available on serious adverse events for tafamidis.

Appendix F. Health-related quality of life

As mentioned in the main body of this application, EQ-5D data was collected as an exploratory endpoint in both ATTRibute-CM and ATTR-ACT trials. These data however were not possible to include in the comparative analyses performed because the ATTR-ACT trial only reported EQ-5D data for the pooled tafamidis dose. However, the collected data in both trials are summarized below.

F.1 EQ-5D-5L data available for ATTRibute-CM

Table 57 summarizes the EQ-5D-5L data available for the ATTRibute-CM trial. At Month 30, a statistically significant (nominal p < 0.0001) and clinically meaningful treatment benefit on EQ-5D-5L VAS was observed favoring acoramidis, with a 10 point change from baseline LS mean difference observed between the two treatment groups (Table 57) (46).

Table 57 Analysis of Change From Baseline in EQ-5D-5L VAS at Month 30 – MMRM (with J2R), mITT Population

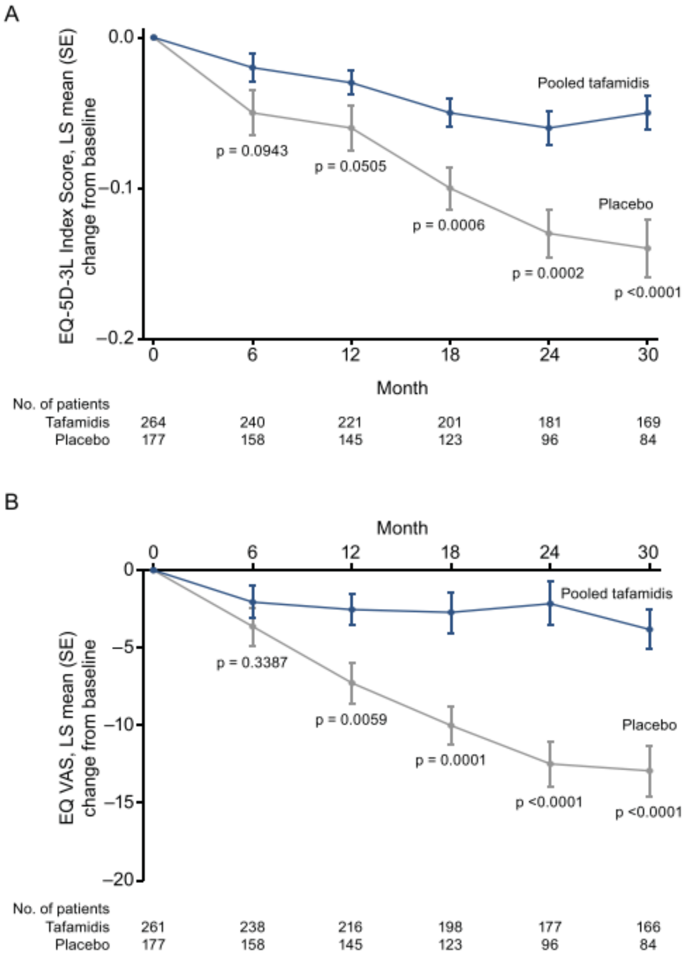
	Acoramidis (N = 409)	Placebo (N=202)
Month 30		
Change From Baseline		
n	402	200
Least Squares Mean	-10.12	-19.66
Standard Error	1.21	1.679
95% CI	-12.49,-7.74	-22.95,-16.37
96% CI	-12.60,-7.63	-23.11,-16.21
LS Mean Difference: Active Dose - Placebo	9.55	
SE for Difference	2.062	
95% CI for difference	5.50, 13.59	
96% CI for difference	5.31,13.78	
p value	<0.0001	

Abbreviations: EQ-5D-5L, EuroQol 5-dimensions 5-levels Health Outcomes Assessment; CI, confidence interval; J2R, Jump to Reference; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; SE, standard error; VAS, visual analog scale.
Source: (46).

F.2 EQ-5D-3L data available for ATTR-ACT

Figure 12 shows the identified EQ-5D-3L data for the ATTR-ACT trial published by Hanna et al, 2021. Tafamidis significantly reduced the decline in EQ-5D-3L Index Score from month 18 (Figure 12), with a least-squares mean difference (95% confidence interval) compared with placebo at month 30 of 0.09 (0.05 to 0.12); p <0.0001. Tafamidis also significantly reduced the decline in EQ VAS from month 12 (Figure 12), with a least-squares mean difference (95% confidence interval) compared with placebo at month 30 of 9.11 (5.39 to 12.83); p <0.0001 (80).

Figure 12 LS mean change (SE) in (A) EQ-5D-3L Index Score and (B) EQ VAS from baseline



Abbreviations: LS, least squares; SE, standard error.
Source: (80).

Appendix G. Probabilistic sensitivity analyses

Not applicable.

Table 58. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Not applicable				

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Objective of the literature search: The main study objective was to conduct a systematic literature review (SLR) of the available literature on clinical efficacy, safety, quality of life, economic burden, and economic value of treatments in patients with wild-type or variant transthyretin amyloid cardiomyopathy (ATTR-CM) (81).

Searches were conducted independently for each scope topic (clinical, economic evaluations, costs and healthcare resource use, and utilities), with results of the literature search also being presented by scope topic. The clinical search, as presented below in this Sections, included efficacy, safety and HRQoL outcomes in its inclusion criteria. These are the only relevant endpoints presented in this application and therefore, the methods and results for the other scope topics (economic evaluations, costs and healthcare resource use, and utilities) were not presented here.

Databases/other sources: Systematic literature searches were conducted on November 23, 2023 in Ovid (http://ovidsp.ovid.com/) to identify peer-reviewed studies of interest in the bibliographic databases listed in Table 59. Searches were complemented by various sources of grey literature as listed in Table 60 and of conferences as listed in Table 61. Hand searches for conference abstracts were conducted for those conferences not already indexed and captured in the Embase searches. Searches were conducted independently for each scope topic (clinical, economic evaluations, costs and healthcare resource use, and utilities) (81).

The presented SLR was considered appropriate as it was conducted approximately one year before the submission date of this application.

Table 59 Bibliographic databases included in the literature search (clinical search)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase via Ovid	http://ovidsp.ovid.com/	No restriction	23.11.2023
Medline and MEDLINE In-Process via Ovid	http://ovidsp.ovid.com/	No restriction	23.11.2023
CENTRAL	http://ovidsp.ovid.com/	No restriction	23.11.2023
CDSR	http://ovidsp.ovid.com/	No restriction	23.11.2023

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled trials.

Source: (81).

Table 60 Other sources included in the literature search (clinical search)

Source name	Location/source	Search strategy	Date of search
Registries of ongoing clinical trials (ClinicalTrials.gov)	https://clinicaltrials.gov/	No restriction	23.11.2023
Registries of ongoing clinical trials (WHO)	https://www.who.int/clinical-trials-registry-platform	No restriction	23.11.2023
Hand-searching of the bibliographies of up to five relevant SLRs	NR	No restriction	23.11.2023

Abbreviations: NR, Not reported; WHO, World Health Organization.

Source: (81).

Table 61 Conference material included in the literature search (clinical search)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference proceedings of ACC from the last two years	NR	Via Embase search	NR	23.11.2023
Conference proceedings of AHA from the last two years	NR	Via Embase search	NR	23.11.2023
Conference proceedings of ESC from the last two years	NR	Via Embase search	NR	23.11.2023
Conference proceedings of ESCHF from the last two years	NR	Hand search	NR	23.11.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference proceedings of HFSA from the last two years	NR	Via Embase search	NR	23.11.2023
Conference proceedings of ISA from the last two years	NR	Hand search	NR	23.11.2023

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESCHF, European Society of Cardiology-Heart Failure; HFSA, Heart Failure Society of America; ISA, International Society of Amyloidosis; NR, Not reported.

Source: (81).

H.1.1 Search strategies

Search strategies

Searches were conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database as recommended by the Cochrane Collaboration (82, 83). The search strings were developed using guideline-recommended filters for specific search platforms to identify studies of relevant design for the different scope topics (84-87).

Searches were restricted to studies conducted in humans and published in English.

Inclusion and exclusion criteria are presented in Table 66.

The exact search strings used in the search per database are presented in Table 62 - Table 65.

Table 62 of search strategy table for Clinical SLR - Embase

No.	Query	Results
1	exp ATTR amyloidosis/	5166
2	(ATTR or hATTR or wtATTR or transthyretin amyloidosis).mp.	5990
3	1 or 2	7702
4	(cardiomyopath$ or cardiac).mp.	1263877
5	3 and 4	4279
6	(ATTR-CM or hATTR-CM or wtATTR-CM).mp.	468
7	5 or 6	4283

No.	Query	Results
8	tafamidis/	1378
9	(tafamidis or fx-1006a or fx1006a or pf-06291826 or pf-6291826 or pf06291826 or pf6291826 or vyndamax or vyndaqel or vyndaquel).ti,ab,tn.	949
10	inotersen/	465
11	(inotersen or gsk 2998728 or gsk2998728 or ionis-ttr-rx or ionis-ttrrx or isis-420915 or isis420915 or isis-gsk1rx or isisgsk1rx or isis-ttr-rx or isis-ttrrx or tegsedi).ti,ab,tn.	315
12	patisiran/	918
13	(patisiran or aln-18328 or aln-ttr02 or aln18328 or alnttr02 or genz-438027 or genz438027 or onpattro or sar-438037 or sar438037).ti,ab,tn.	662
14	vutrisiran/	129
15	(vutrisiran or aln-65492 or aln-ttrsc02 or aln65492 or alnttrsc02 or amvuttra or votrisiran).ti,ab,tn.	68
16	acoramidis/	59
17	(acoramidis or ag-10 or ag10 or alxn-2060 or alxn2060 or bbp-265 or bbp265).ti,ab,tn.	374
18	diflunisal/	3043
19	(diflunisal or adomal or algobid or analeric or ansal or biartac or citidol or diflonid or diflunil or diflusal or dolibid or dolobid or dolobis or dolocid or donobid or dorbid or flovacil or flunidor or fluniget or fluodomil or fluodonil or flustar or ilacen or mk-647 or mk647 or reuflos or sv-108 or sv108 or unisal).ti,ab,tn.	1429
20	exp organ transplantation/	468407
21	(transplant$ or graft$).ti,ab,kw.	1158953
22	eplontersen/	56
23	(eplontersen or akcea-ttr-lrx or akcea-ttrlrx or ion-682884 or ion682884 or ionisttr-lrx or ionis-ttrlrx or ionis-ttr-lrx or isis-682884 or isis682884).ti,ab,tn.	37
24	or/8-23	1241013
25	7 and 24	1535
26	Clinical Trial/	1075596

No.	Query	Results
27	Randomized Controlled Trial/	793462
28	controlled clinical trial/	471457
29	multicenter study/	378848
30	Phase 3 clinical trial/	70650
31	Phase 4 clinical trial/	5503
32	exp RANDOMIZATION/	99345
33	Single Blind Procedure/	52461
34	Double Blind Procedure/	212684
35	Crossover Procedure/	75938
36	PLACEBO/	405202
37	randomi?ed controlled trial$.tw.	330976
38	rct.tw.	55041
39	(random$ adj2 allocat$).tw.	55601
40	single blind$.tw.	32129
41	double blind$.tw.	246716
42	((treble or triple) adj blind$).tw.	1972
43	placebo$.tw.	370673
44	Prospective Study/	894384
45	(single-arm or non-random$ or nonrandom$ or single-group).tw.	98088
46	pooled analy$.tw.	23924
47	(open-label and extension$).tw.	9737
48	or/26-47	3041929
49	Case Study/	98040
50	case report.tw.	549580
51	abstract report/ or letter/	1307616

No.	Query	Results
52	Conference proceeding.pt.	0
53	Editorial.pt.	786520
54	Letter.pt.	1297055
55	Note.pt.	965193
56	or/49-55	3771580
57	48 not 56	2897383
58	25 and 57	363
59	58 not ((exp animal/ or nonhuman/) not exp human/)	355
60	59 not conference abstract.pt.	143
61	limit 60 to yr="2013-current"	129
62	limit 59 to (conference abstract and yr="2021-current")	74
63	61 or 62	203

Source: (81).

Table 63 of search strategy table for Clinical SLR - MEDLINE

No.	Query	Results
1	(ATTR or hATTR or wtATTR or transthyretin amyloidosis).mp.	2689
2	(cardiomyopath$ or cardiac).mp.	953900
3	1 and 2	1524
4	(ATTR-CM or hATTR-CM or wtATTR-CM).mp.	209
5	3 or 4	1525
6	tafamidis.nm.	212
7	(tafamidis or fx-1006a or fx1006a or pf-06291826 or pf-6291826 or pf06291826 or pf6291826 or vyndamax or vyndaqel or vyndaquel).ti,ab,kw.	432
8	inotersen.nm.	47
9	(inotersen or gsk 2998728 or gsk2998728 or ionis-ttr-rx or ionis-ttrrx or isis-420915 or isis420915 or isis-gsk1rx or isisgsk1rx or isis-ttr-rx or isis-ttrrx or tegsedi).ti,ab,kw.	125

No.	Query	Results
10	patisiran.nm.	82
11	(patisiran or aln-18328 or aln-ttr02 or aln18328 or alnttr02 or genz-438027 or genz438027 or onpattro or sar-438037 or sar438037).ti,ab,kw.	258
12	(vutrisiran or aln-65492 or aln-ttrsc02 or aln65492 or alnttrsc02 or amvuttra or votrisiran).ti,ab,kw.	26
13	(acoramidis or ag-10 or ag10 or alxn-2060 or alxn2060 or bbp-265 or bbp265).ti,ab,kw.	283
14	diflunisal/	540
15	(diflunisal or adomal or algobid or analeric or ansal or biartac or citidol or diflonid or diflunil or diflusal or dolibid or dolobid or dolobis or dolocid or donobid or dorbid or flovacil or flunidor or fluniget or fluodomil or fluodonil or flustar or ilacen or mk-647 or mk647 or reuflos or sv-108 or sv108 or unisal).ti,ab,kw.	821
16	exp organ transplantation/	238307
17	(transplant$ or graft$).ti,ab,kw.	811943
18	(eplontersen or akcea-ttr-lrx or akcea-ttrlrx or ion-682884 or ion682884 or ionisttr-lrx or ionis-ttrlrx or ionis-ttr-lrx or isis-682884 or isis682884).ti,ab,kw.	13
19	or/6-18	849836
20	5 and 19	415
21	Randomized Controlled Trials as Topic/	165492
22	randomized controlled trial/	603937
23	Random Allocation/	107042
24	Double Blind Method/	176733
25	Single Blind Method/	33084
26	clinical trial/	539104
27	clinical trial, phase i.pt.	25390
28	clinical trial, phase ii.pt.	40532
29	clinical trial, phase iii.pt.	22207

No.	Query	Results
30	clinical trial, phase iv.pt.	2458
31	controlled clinical trial.pt.	95471
32	randomized controlled trial.pt.	603937
33	multicenter study.pt.	340282
34	clinical trial.pt.	539104
35	exp Clinical Trials as topic/	386292
36	pooled analy$.tw.	15028
37	(open-label and extension$).tw.	3316
38	or/21-37	1596216
39	(clinical adj trial$).tw.	494156
40	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	201037
41	PLACEBOS/	35934
42	placebo$.tw.	251354
43	randomly allocated.tw.	37391
44	(allocated adj2 random$).tw.	41230
45	or/39-44	803028
46	38 or 45	1954370
47	case report.tw.	409941
48	letter/	1236355
49	historical article/	369446
50	or/47-49	1996309
51	46 not 50	1911050
52	20 and 51	112
53	52 not (exp animals/ not exp humans/)	111
54	limit 53 to yr="2013-current"	107

Source: (81).

Table 64 of search strategy table for Clinical SLR - Cochrane Central Register of Controlled Trials

No.	Query	Results
1	(ATTR or hATTR or wtATTR or transthyretin amyloidosis).mp.	310
2	(cardiomyopath$ or cardiac).mp.	78834
3	1 and 2	193
4	(ATTR-CM or hATTR-CM or wtATTR-CM).mp.	67
5	3 or 4	194
6	(tafamidis or fx-1006a or fx1006a or pf-06291826 or pf-6291826 or pf06291826 or pf6291826 or vyndamax or vyndaqel or vyndaquel).ti,ab,kw.	154
7	(inotersen or gsk 2998728 or gsk2998728 or ionis-ttr-rx or ionis-ttrrx or isis-420915 or isis420915 or isis-gsk1rx or isisgsk1rx or isis-ttr-rx or isis-ttrrx or tegsedi).ti,ab,kw.	90
8	(patisiran or aln-18328 or aln-ttr02 or aln18328 or alnttr02 or genz-438027 or genz438027 or onpattro or sar-438037 or sar438037).ti,ab,kw.	115
9	(vutrisiran or aln-65492 or aln-ttrsc02 or aln65492 or alnttrsc02 or amvuttra or votrisiran).ti,ab,kw.	29
10	(acoramidis or ag-10 or ag10 or alxn-2060 or alxn2060 or bbp-265 or bbp265).ti,ab,kw.	24
11	(diflunisal or adomal or algobid or analeric or ansal or biartac or citidol or diflonid or diflunil or diflusal or dolibid or dolobid or dolobis or dolocid or donobid or dorbid or flovacil or flunidor or fluniget or fluodomil or fluodonil or flustar or ilacen or mk-647 or mk647 or reuflos or sv-108 or sv108 or unisal).ti,ab,kw.	246
12	(transplant$ or graft$).ti,ab,kw.	60902
13	(eplontersen or akcea-ttr-lrx or akcea-ttrlrx or ion-682884 or ion682884 or ionisttr-lrx or ionis-ttrlrx or ionis-ttr-lrx or isis-682884 or isis682884).ti,ab,kw.	21
14	or/6-13	61463
15	5 and 14	169
16	limit 15 to yr="2013-current"	162

Source: (81).

Table 65 of search strategy table for Clinical SLR - Cochrane Database of Systematic Reviews

No.	Query	Results
1	(ATTR or hATTR or wtATTR or transthyretin amyloidosis).mp.	2
2	(cardiomyopath$ or cardiac).mp.	2087
3	1 and 2	2
4	(ATTR-CM or hATTR-CM or wtATTR-CM).mp.	0
5	3 or 4	2
6	(tafamidis or fx-1006a or fx1006a or pf-06291826 or pf-6291826 or pf06291826 or pf6291826 or vyndamax or vyndaqel or vyndaquel).ti,ab,kw.	1
7	(inotersen or gsk 2998728 or gsk2998728 or ionis-ttr-rx or ionis-ttrrx or isis-420915 or isis420915 or isis-gsk1rx or isisgsk1rx or isis-ttr-rx or isis-ttrrx or tegsedi).ti,ab,kw.	1
8	(patisiran or aln-18328 or aln-ttr02 or aln18328 or alnttr02 or genz-438027 or genz438027 or onpattro or sar-438037 or sar438037).ti,ab,kw.	1
9	(vutrisiran or aln-65492 or aln-ttrsc02 or aln65492 or alnttrsc02 or amvuttra or votrisiran).ti,ab,kw.	0
10	(acoramidis or ag-10 or ag10 or alxn-2060 or alxn2060 or bbp-265 or bbp265).ti,ab,kw.	0
11	(diflunisal or adomal or algobid or analeric or ansal or biartac or citidol or diflonid or diflunil or diflusal or dolibid or dolobid or dolobis or dolocid or donobid or dorbid or flovacil or flunidor or fluniget or fluodomil or fluodonil or flustar or ilacen or mk-647 or mk647 or reuflos or sv-108 or sv108 or unisal).ti,ab,kw.	7
12	(transplant$ or graft$).ti,ab,kw.	563
13	(eplontersen or akcea-ttr-lrx or akcea-ttrlrx or ion-682884 or ion682884 or ionisttr-lrx or ionis-ttrlrx or ionis-ttr-lrx or isis-682884 or isis682884).ti,ab,kw.	0
14	or/6-13	570
15	5 and 14	1
16	limit 15 to yr="2013-current"	1

Note: total: 473; deduped: 354.

Source: (81).

H.1.2 Systematic selection of studies

The resulting titles and abstracts were imported to EndNote 21, where citations identified from more than one database were removed as duplicates. Following de-duplication, the search results were uploaded to Nested Knowledge software. Nested Knowledge is a semi-automated, internet-based program that facilitates collaboration among reviewers during the study selection process. Separate EndNote libraries and Nested Knowledge projects were generated for the SLR (81).

The study selection process involved evaluating publications retrieved by the searches against predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria (Table 66) to establish which studies were eligible for inclusion in the SLR (81).

Table 66 Inclusion and exclusion criteria used for assessment of studies (clinical)

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria	Changes, local adaption
Population	• Adult (≥18 years) patients with ATTR-CM with wild-type or variant genotype • Subgroups based on NYHA class or NAC stage	Patients without ATTR-CM	None
Interventions	• Acoramidis (AG10) • Tafamidis • Inotersen • Patisiran • Vutrisiran • Diflunisal • Eplontersen • Organ transplant	Non-pharmacological interventions other than organ transplant (e.g., supplements)	Of the overall results for the clinical search, only those pertaining to relevant interventions in Danish clinical practice were included in this application. The chosen interventions were validated by Danish clinical expert opinion (36, 37).
Comparators	None required	NA	None
Outcomes	Efficacy • Overall survival • CV-related mortality • All-cause hospitalizations • CV-related hospitalizations (including urgent HF visits) • Functional exercise capacity (e.g., 6MWT)	Outcomes not of interest	None

	• Cardiac biomarkers (BNP level, Troponin, eGFR) • Signs and symptoms of heart failure (such as breathlessness, or NYHA class or NAC stage) • Serum TTR • Cardiac imaging in ATTR population (ECHO, PET-scan, CMR) • Change in LV wall thickness • Change in LV GLS Safety • Total AEs • Total serious AE • Discontinuations due to AEs • Drug-related AEs HRQoL • General instruments (e.g., EQ-5D, SF-36) • Disease-specific instruments (e.g., KCCQ) • Patient and caregiver HRQoL		
Study design/Publication type	• Clinical trials (RCTs, non-RCTs, and single-arm trials) • Pooled analyses of trials • Open-label extensions of trials • SLRs/MAs	• Narrative reviews, study protocols, case reports, editorials, letters, animal, cellular, molecular, genetic or pharmacokinetics studies • Observational studies	None
Language restrictions	• English		None
Geographical regions	• None		None

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; ATTR, transthyretin amyloid; ATTR-CM, transthyretin amyloid cardiomyopathy; BNP, brain natriuretic peptide; CMR, cardiovascular magnetic resonance; CV, cardiovascular; ECHO, echocardiogram; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HF, heart failure; HRQoL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MA, meta-analysis; NA, not applicable; NAC, National Amyloidosis Centre;

NYHA, New York Heart Association; PET, positron emission tomography; RCT, randomized controlled trial; SF-36, 36-item Short Form Health Survey; SLR, systematic literature review; TTR, transthyretin

Source: (81).

H.1.2.1 Title and Abstract Screening

In the first stage of screening, two reviewers independently assessed the title and abstract of each publication to determine its eligibility for inclusion in the SLR, according to the PICOS criteria (Table 66). A third reviewer resolved any disagreements (81).

Detailed screening rules were prepared so that titles and abstracts were excluded or included in a systematic manner. The screening commenced with a calibration exercise that piloted and refined the screening rules (81).

H.1.2.2 Full-text Screening

In the second pass of screening, two independent reviewers screened the full-text articles from the included abstracts. A third reviewer resolved any disagreements. Considering the inclusion and exclusion criteria, studies were designated as excluded or included. For each excluded study, a specific reason for the exclusion was selected (81).

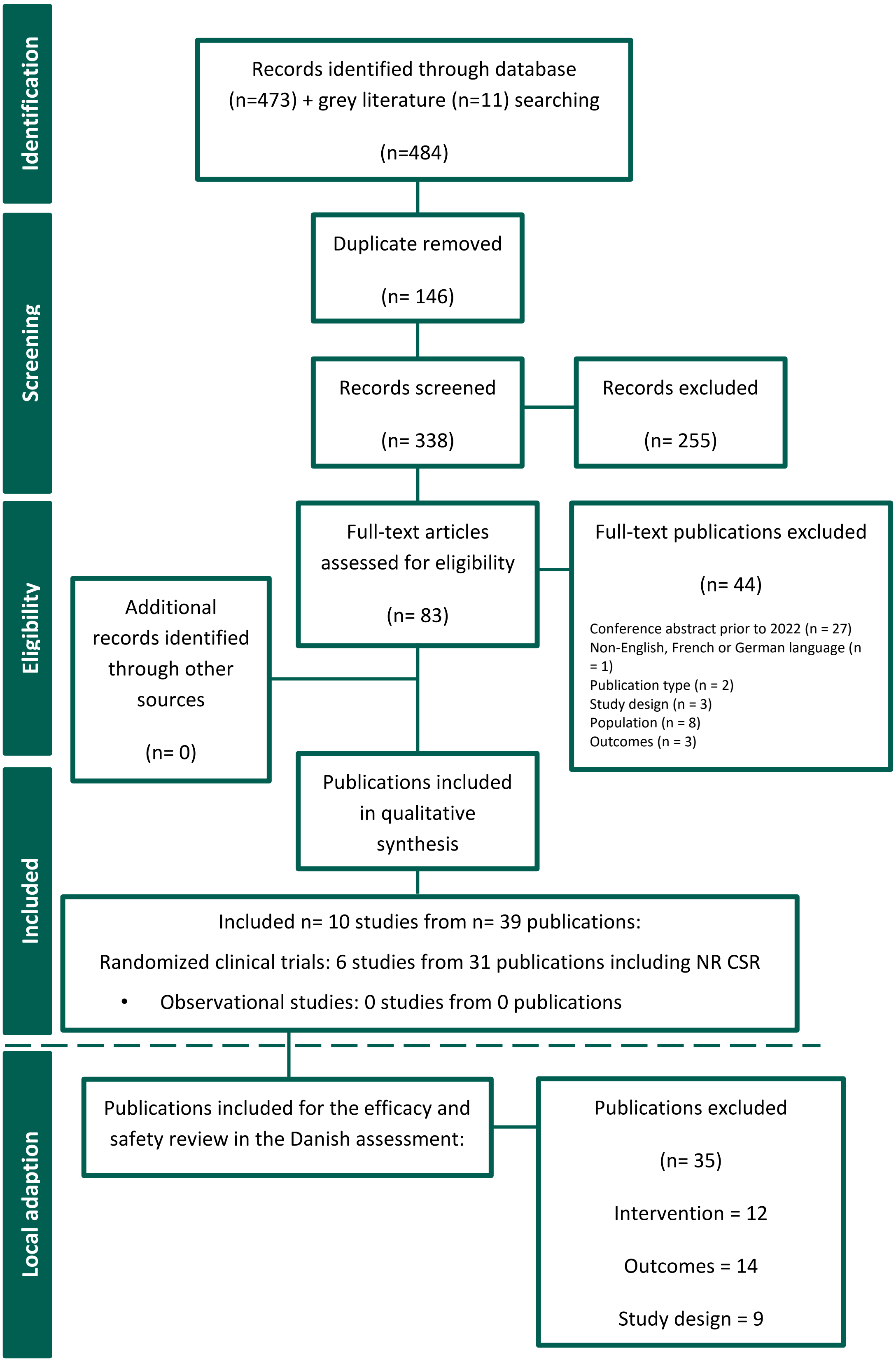
H.1.2.3 Study Listing and PRISMA Diagram

Following completion of the full-text screening, a study listing was generated in Microsoft Excel®, including a list of accepted primary studies (and their related publications) with relevant study tags, articles excluded at full-text screening organized by reasons for exclusion, and the full list of studies reviewed at the abstract screening level (81).

A PRISMA flow diagram was also generated with Nested Knowledge, displaying the number of included and excluded publications at each stage (searches, de-duplication, title and abstract screening, full-text screening), with the reasons for exclusion at the full-text screening level listed (Figure 13) (81).

Any relevant publications identified through the SLR bibliography quality assurance step were included, and their inclusion was recorded separately in the PRISMA diagrams—thus ensuring transparency and replicability (81).

Figure 1 PRISMA diagram (clinical search)


Identification
Records identified through database (n=473) + grey literature (n=11) searching
(n=484)
Screening
Duplicate removed
(n= 146)
Records screened
(n= 338)
Records excluded
(n= 255)
Eligibility
Full-text articles assessed for eligibility
(n= 83)
Full-text publications excluded
(n= 44)
Conference abstract prior to 2022 (n = 27)
Non-English, French or German language (n = 1)
Publication type (n = 2)
Study design (n = 3)
Population (n = 8)
Outcomes (n = 3)
Additional records identified through other sources
(n= 0)
Included
Publications included in qualitative synthesis
Included n= 10 studies from n= 39 publications:
Randomized clinical trials: 6 studies from 31 publications including NR CSR
• Observational studies: 0 studies from 0 publications
Local adaption
Publications included for the efficacy and safety review in the Danish assessment:
Publications excluded
(n= 35)
Intervention = 12
Outcomes = 14
Study design = 9

H.1.2.4 Studies included in the analyses

The searches for all databases were conducted on November 23, 2023, and yielded 473 records. In addition, 11 records were retrieved from grey literature. After removing duplicates, 338 were screened. Following title and abstract screening, 83 abstracts were deemed potentially relevant and assessed at the full-text level, resulting in 39 included publications reporting on 10 trials. Figure 13 summarizes the flow of studies included in the clinical SLR. One record reporting on the ATTRibute-CM trial is included in the report although it was published after the search cut-off (total of 11 trials) (81).

This section provides an overview of 11 unique studies conducted in patients with ATTR-CM, encompassing variant and wild-type genotypes. These studies consist of randomized controlled trials (RCTs) (n=4) (51, 88-90), single-arm trials (n=4) (91-94), and open-label, long-term extension (LTE) studies (n=3) (95-97). Among these, the most recent were the phase 3 RCTs, namely ATTRibute-CM (2024) (90), APOLLO-B (2023) (88), and ATTR-ACT (2018) (51) and its LTE (2022) (95), followed by the phase 2 RCT, Study of AG10 (2019)(89) and its LTE (2022) (96). The remaining trials are the single-arm trials, DFNS-02 (2022) (93), INOCARD (2022) (92), Dasgupta et al (2020) (91), and Fx1B-201 (94) with a phase 3 LTE (2021) (97). The enrollment period in the primary studies ranged from 2008 (94) to 2021. More information on the study characteristics for the clinical SLR can be found in Table 67.

Inclusion criteria typically involved patients with a confirmed diagnosis of ATTR-CM, evidence of cardiac involvement, and a history of heart failure. Several studies, including the older tafamidis trials (51, 94) and inotersen study (91), required biopsy to diagnose transthyretin amyloidosis (ATTR), whereas newer studies of patisiran and acoramidis determined diagnosis based on biopsy or imaging (88-90). Exclusion criteria often involved factors such as other types of heart failure, certain medical conditions, or prior treatments.

The interventions studied included tafamidis (ATTR-ACT (51) and its LTE (95) and Fx1B-201 (94) and its LTE (97)), patisiran (APOLLO-B) (88), acoramidis (ATTRibute-CM (90) and Study AG10 (89) and its LTE (96)), inotersen (INOCARD (92) and Dasgupta et al. [2020] (91)), and diflunisal (DFNS-02) (93).

Table 67 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Apollo-B (NCT03997383)	To present the primary efficacy and safety data from the 12-month double-blind period of the	RCT, phase 3	Patients with ATTR-CA	Patisiran (n=181) vs	Primary outcome: NR; Treatment	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	APOLLO-B trial, a phase 3, randomized, placebo-controlled trial involving patients with variant or wild-type ATTR cardiac amyloidosis			Placebo (n=178)	duration: 12 months	
ATTR-ACT (NCT01994889)	To determine the efficacy and safety of tafamidis in patients with hereditary and wild type transthyretin amyloid cardiomyopathy.	RCT, phase 3	Patients with ATTR-CM (hereditary or wild type)	Tafamidis 80 or 20 mg (n=264) vs Placebo (n=177)	Primary outcome: NR; Treatment duration: 30 months	NR
ATTR-ACT LTE (NCT01994889	To assess long-term efficacy of tafamidis from an ongoing long-term extension (LTE) to the pivotal ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial).	NR	Patients with ATTR-CM (hereditary or wild type)	Tafamidis 61 mg (n=176) vs Placebo (n=177)	Primary outcome: NR; Treatment duration: up to 60 months	
ATTRibute-CM (NCT03860935)	To evaluate acoramidis in Transthyretin Amyloid Cardiomyopathy	RCT, phase 3	Patients with transthyretin amyloid cardiomyopathy	Acoramids 800 mg (n=421) vs Placebo (n=211)	Primary outcome: NR; Treatment duration: 30 months	NR
OLE for AG10 phase 2	To report an update on long-term outcomes in the open-label extension (OLE) study of the phase 2 study on AG10	RCT, phase 2, OLE	Patients with symptomatic TTR amyloid cardiomyopathy (ATTR-CM)	Acoramids 800 mg (n=47)	Primary outcome: NR; Treatment duration: NR	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study of AG10 in Amyloid Cardiomyopathy (NCT03458130)	To evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of AG10 in ATTR-CM patients with symptomatic, chronic heart failure	RCT, phase 2	Patients with ATTR-CM aged 18 to 90 years and with NYHA functional class II to III symptoms	Acoramids 800 mg (n=16) vs Acoramids 400 mg (n=16) vs Placebo (n=17)	Primary outcome: NR; Treatment duration: 28 days	NR
Dasgupta, 2020	To evaluate the long term safety and efficacy of transthyretin specific antisense oligonucleotide therapy, inotersen, in transthyretin cardiomyopathy.	Single-arm, open-label	Patients with hereditary or wild-type ATTR	Inotersen 300mg/1.5ml (n=33)	Primary outcome: NR; Treatment duration: 24 months)	NR
DFNS-02	To monitor the effect of diflunisal in patients with ATTRv amyloidosis	Single-arm, open-label	Patient with ATTRv amyloidosis	Diflunisal 500 mg (n=33)	Primary outcome: NR; Treatment duration: 24 months	NR
INOCARD	To evaluate the efficacy and safety of inotersen for TTR cardiomyopathy	Single-arm, open-label	Patients with ATTR	Inotersen 300mg (n=31)	Primary outcome: NR; Treatment duration: up to 24 months	NR
Fx1B-201 (NCT00694161)	To evaluate the safety of oral tafamidis treatment and effects on TTR stability in patients with wild-type or V122I TTR-	Single-arm, open-label	Patients with wild-type ATTR-CM	Tafamidis 20mg (n=31)	Primary outcome: NR; Treatment duration: 12 months	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	CM. Many exploratory efficacy variables were also assessed.					
Fx1B-201 LTE (NCT00935012)	To assess safety and efficacy evaluation of Fx-1006a in patients with V122i or wild-type transthyretin (TTR) amyloid cardiomyopathy	Single-arm, open-label, phase 3	Adult (18-75 years) patients with V122i or wild-type ATTR-CM	Tafamidis 20mg (n=31)	Primary outcome: NR; Treatment duration: up to 10 years	NR

Abbreviations: ATTR-CM, Transthyretin amyloid cardiomyopathy; LTE, Long-term extension; NR, Not reported; NYHA, New York Heart Association; RCT, Randomized clinical trial; TTR, Transthyretin.

Source: (81).

Local adaptation

Of the included studies in the SLR listed in Table 67, only two studies were considered relevant in this application (comprised of four publications). The included studies were phase 3 RCTs for acoramidis and tafamidis, the ATTRibute-CM (2024) (90) and ATTR-ACT (2018) (51) trials, respectively. The decision of study inclusion in the local adaptation of the SLR was guided by the relevant comparator in Danish clinical practice, as well as relevant outcomes reported. The chosen comparator, tafamidis, was validated during consultation with DMC, as well as by Danish clinical expert opinion (36, 37) and guidelines (38).

Hence, there were 8 studies and 35 publications excluded. The ATTR-ACT long-term extension (LTE) (2022) (95), as well as phase 2 RCT for acoramidis, Study of AG10 (2019) (89) and its LTE (2022) (96) were excluded due to their study design not being of interest (comprised of nine publications). The remaining studies APOLLO-B (2023) (88), DFNS-02 (2022) (93), INOCARD (2022) (92), Dasgupta et al (2020) (91), and Fx1B-201 (94) with a phase 3 LTE (2021) (97) were excluded due to the intervention not being of interest (comprised of 12 publications). Additionally, there were 14 publications excluded due to the outcomes reported not being of interest. No further local adaptations were done, as the SLR search was conducted with no geographical restriction, hence capturing all relevant evidence available (Danish studies, if available, would have also been identified).

The local adaptation included therefore four publications which were Gillmore et al. 2024 (ATTRibute-CM), as well as Damy et al. 2021, Maurer et al. 2028 and Hanna et al. 2021 (ATTR-ACT). It is important to note that data reported in Maurer et al. and Hanna et al. were only included in appendix in this application (Kaplan Meier for ACM and HRQoL data, respectively).

H.1.3 Excluded full-text references

Table 68 list all the full-text references excluded with respective reasons for exclusion from the clinical SLR search (81).

Table 68 List of excluded full-text references

Citation	Reason for exclusion
Adams D, Coelho T, Conceicao I, et al. Phase 2 open-label extension (OLE) study of patisiran for the treatment of hereditary ATTR (hATTR) amyloidosis: 24-month safety and efficacy in subgroup of patients with cardiac involvement. 2017;19:19. doi:10.1002/ejhf.833.	Excluded: Exclude: Conference abstract published prior to 2022
Berk J, Damy T, Drachman B, et al. Efficacy of Tafamidis in Transthyretin Amyloid Cardiomyopathy in the ATTR-ACT Trial. 2020;49(2):209. doi:10.1016/j.hrtlng.2020.02.009.	Excluded: Exclude: Conference abstract published prior to 2022
Coelho T, Adams D, Conceicao I, et al. A phase II, open-label, extension study of long-term patisiran treatment in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. Orphanet journal of rare diseases. 2020;15(1):179. doi:10.1186/s13023-020-01399-4.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Damy T, Elliott P, Gundapaneni B, See Tai S, Sultan MB, Drachman BM. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. 2020;41(SUPPL 2):2142. doi:10.1093/ehjci/ehaa946.2142.	Excluded: Exclude: Conference abstract published prior to 2022
Damy T, Fine N, Gundapaneni B, Sultan MB, Grogan M. Safety of Transition from Tafamidis Meglumine 20 Mg to Tafamidis Free Acid 61 Mg in Patients with Transthyretin Amyloid Cardiomyopathy. 2020;142(SUPPL 3). doi:10.1161/circ.142.suppl3.12896.	Excluded: Exclude: Conference abstract published prior to 2022
Damy T, Judge D, Kristen A, 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. Journal of cardiovascular translational research. 2015;8(2):117-27. doi:10.1007/s12265-015-9613-9.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)

Dasgupta NR, Falk RH, Drachman BM, et al. SAFETY OF INOTERSEN TREATMENT IN PATIENTS WITH TRANSTHYRETIN AMYLOID CARDIOMYOPATHY. 2019;73(9 Supplement 1):909. doi:10.1016/s0735-1097(19)31516-5.	Excluded: Exclude: Conference abstract published prior to 2022
Elliott P, Drachman BM, Gottlieb SS, et al. Interim analysis of data from a long-term, extension trial of tafamidis meglumine in patients with transthyretin amyloid cardiomyopathy. 2019;40:645. doi:10.1093/eurheartj/ehz748.0011.	Excluded: Exclude: Conference abstract published prior to 2022
Fox JC, Heitner S, Falk R, et al. AG10 CONSISTENTLY STABILIZES TRANSTHYRETIN TO A HIGH LEVEL IN BOTH WILD TYPE AND MUTANT AMYLOID CARDIOMYOPATHY: RESPONDER ANALYSES FROM A PHASE 2 CLINICAL TRIAL. 2019;73(9 Supplement 1):660. doi:10.1016/s0735-1097(19)31268-9.	Excluded: Exclude: Conference abstract published prior to 2022
Garcia-Pavia P, Fine N, Weissman NJ, et al. Patients with transthyretin amyloid cardiomyopathy may have preserved, mildly reduced, or reduced ejection fraction. 2021;42(SUPPL 1):717. doi:10.1093/eurheartj/ehab724.0717.	Excluded: Exclude: Study design not of interest (animal, cellular, molecular, genetic or pharmacokinetics studies, observational studies)
Grogan M, Witteles R, Shah SJ, et al. Efficacy of Tafamidis in Patients with Hereditary or Wild-Type Transthyretin Amyloid Cardiomyopathy: further Results from the ATTR-ACT Trial. 2019;38(4):S204. doi:10.1016/j.healun.2019.01.493.	Excluded: Exclude: Conference abstract published prior to 2022
Hanna M, Stewart M, Gundapaneni B, et al. Tafamidis Reduced the Decline in Health-Related Quality of Life in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). 2019;25(8):S7. doi:10.1016/j.cardfail.2019.07.024.	Excluded: Exclude: Conference abstract published prior to 2022
Hanna M, Fine N, Stewart M, Gundapaneni B, Sultan MB, Witteles R. Functional Capacity, Health-related Quality-of-life and Cardiac Biomarker Improvement with Tafamidis in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). 2020;26(10):S65. doi:10.1016/j.cardfail.2020.09.191.	Excluded: Exclude: Conference abstract published prior to 2022
Hanna M.A., Fine N., Gundapaneni B., Sultan M.B., Witteles R. Improvement in measures of disease progression with tafamidis in the tafamidis in transthyretin cardiomyopathy clinical trial (ATTR-ACT). Circulation. 2021;144(SUPPL 1). doi:10.1161/circ.144.suppl_1.12239.	Excluded: Exclude: Conference abstract published prior to 2022
Judge DP, Falk R, Grogan M, et al. Safety, tolerability and transthyretin stabilization by AG10: a phase 2, randomized, double-blind, placebo-controlled clinical trial in patients with transthyretin amyloid cardiomyopathy and nyha class II/III heart failure. 2018;138(25):e770. doi:10.1161/cir.0000000000000636.	Excluded: Exclude: Conference abstract published prior to 2022

Li H, Rozenbaum MH, Casey M, Sultan M. Estimating treatment effect of tafamidis on hospitalisation in NYHA class III ATTR-CM patients in the presence of death using principal stratification. 2021;42(SUPPL 1):829. doi:10.1093/eurheartj/ehab724.0829.	Excluded: Exclude: Conference abstract published prior to 2022
Li B, Alvir J, Stewart M. Extrapolation of Survival Benefits in Patients with Transthyretin Amyloid Cardiomyopathy Receiving Tafamidis: Analysis of the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. Cardiology and therapy. 2020;9(2):535-540. doi:10.1007/s40119-020-00179-2.	Excluded: Exclude: Outcomes not of interest
Longhi S, Maurer MS, Fontana M, et al. PRIMARY RESULTS FROM APOLLO-B, A PHASE 3 STUDY OF PATISIRAN IN PATIENTS WITH TRANSTHYRETIN-MEDIATED AMYLOIDOSIS WITH CARDIOMYOPATHY. 2022;24:K224. doi:10.1093/eurheartjsupp/suac121.630.	Excluded: Exclude: Publication type not of interest (narrative reviews, case reports, dissertations, letters, editorials, comments, notes, erratum, and trial protocols)
Masri A, Aras M, Falk RH, et al. LONG-TERM SAFETY AND TOLERABILITY OF ACORAMIDIS (AG10) IN SYMPTOMATIC TRANSTHYRETIN AMYLOID CARDIOMYOPATHY: UPDATED ANALYSIS FROM AN ONGOING PHASE 2 OPEN-LABEL EXTENSION STUDY. 2022;79(9):227. doi:10.1016/s0735-1097(22)01218-9.	Excluded: Exclude: Outcomes not of interest
Maurer MS, Adler E, Gundapaneni B, Sultan MB, Rapezzi C. Efficacy of Tafamidis by Baseline 6-minute Walk Test Distance in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). 2020;26(10):S10. doi:10.1016/j.cardfail.2020.09.037.	Excluded: Exclude: Conference abstract published prior to 2022
Maurer MS, Heitner S, Drachman B, et al. Inotersen improves quality of life in patients with hereditary transthyretin amyloidosis with polyneuropathy and cardiomyopathy: results of the phase 3 study neuro-ttr. 2018;71(11). doi:10.1016/s0735-1097(18)31199-9.	Excluded: Exclude: Conference abstract published prior to 2022
Merlini G, Plante-Bordeneuve V, Judge D, et al. Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis. Journal of cardiovascular translational research. 2013;6(6):1011-20. doi:10.1007/s12265-013-9512-x.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Miller AB, Januzzi J, O'Neill BJ, et al. CAUSES OF CARDIOVASCULAR HOSPITALIZATION AND DEATH IN THE TAFAMIDIS IN TRANSTHYRETIN CARDIOMYOPATHY CLINICAL TRIAL (ATTR-ACT). 2020;75(11):692. doi:10.1016/s0735-1097(20)31319-x.	Excluded: Exclude: Conference abstract published prior to 2022
Minamisawa M, Claggett B, Adams D, et al. Association of Patisiran, an RNA Interference Therapeutic, With Regional Left Ventricular Myocardial Strain in Hereditary Transthyretin Amyloidosis: The APOLLO Study. JAMA cardiology. 2019;4(5):466-472. doi:10.1001/jamacardio.2019.0849.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)

Mussinelli R, Whelan C, Drachman B, et al. Exploratory cardiac measures in patients with severe hereditary transthyretin amyloid cardiomyopathy treated with inotersen in the phase 3 neuro-ttr study. 2020;22(SUPPL G):G82. doi:10.1093/eurheartj/suaa106.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Palecek T, Krejci J. ATTR-ACT study: breakthrough in the treatment of transthyretin cardiac amyloidosis. Studie ATTR-ACT: P&rcaron;elom v l&eacute;&ccaron;b&ecaron; transthyretinov&eacute; srde&ccaron;n&iacute; amyloid&oacute;zy. 2019;18(1):45.	Excluded: Exclude: Non English, French, or German Language
Patel J, Elliott P, Gundapaneni B, Li B, Sultan M, Grogan M. Long-term Survival Benefit of Tafamidis in Patients with Transthyretin Amyloid Cardiomyopathy. 2020;26(10):S64. doi:10.1016/j.cardfail.2020.09.190.	Excluded: Exclude: Conference abstract published prior to 2022
Rapezzi C, Kristen AV, Gundapaneni B, Sultan MB, Hanna M. Benefits of tafamidis in patients with advanced transthyretin amyloid cardiomyopathy. 2020;41(SUPPL 2):2115. doi:10.1093/ehjci/ehaa946.2115.	Excluded: Exclude: Conference abstract published prior to 2022
Rettl R., Duca F., Binder C., et al. Impact of tafamidis on myocardial strain in transthyretin amyloid cardiomyopathy. Amyloid. 2023;30(1):127-137. doi:10.1080/13506129.2022.2131385.	Excluded: Exclude: Study design not of interest (animal, cellular, molecular, genetic or pharmacokinetics studies, observational studies)
Rosenblum H., Griffin J.M., Minamisawa M., et al. Patisiran Stabilizes Cardiac Mechanics in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Post-hoc Analysis of the APOLLO Study. Archives of Cardiovascular Diseases Supplements. 2021;13(3):255. doi:10.1016/j.acvdsp.2021.04.040.	Excluded: Exclude: Conference abstract published prior to 2022
Rosenblum H, Griffin J, Minamisawa M, et al. Effect of patisiran on stroke volume in hereditary transthyretin-mediated amyloidosis: insights from pressure-volume analysis of the APOLLO study. European journal of heart failure. 2023;25(5):727-736. doi:10.1002/ejhf.2783.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Rozenbaum M, Ines M, Young R. POSB426 Long-Term Time-Varying Survival Treatment Effect in the Presence of Scheduled Switch from Placebo to Active Treatment. 2022;25(1):S275. doi:10.1016/j.jval.2021.11.1337.	Excluded: Exclude: Study design not of interest (animal, cellular, molecular, genetic or pharmacokinetics studies, observational studies)
Schumacher J., Gundapaneni B., Riley S., Keohane D., Tai S.S., Sultan M. EVALUATION OF TRANSTHYRETIN TETRAMER STABILIZATION AND TTR PLASMA CONCENTRATIONS IN THE TAFAMIDIS IN TRANSTHYRETIN CARDIOMYOPATHY CLINICAL TRIAL (ATTR-ACT). Journal of the American College of Cardiology.	Excluded: Exclude: Conference abstract published prior to 2022

2021;77(18 Supplement 1):525. doi:10.1016/s0735-1097%2821%2901884-2.	
Shah SJ, Gundapaneni B, Sultan MB, Merlini G. Survival Benefit with Higher Dose Tafamidis in Patients with Hereditary and Wild-type Transthyretin Amyloid Cardiomyopathy. 2020;142(SUPPL 3). doi:10.1161/circ.142.suppl3.13149.	Excluded: Exclude: Conference abstract published prior to 2022
Solomon S, Adams D, Kristen A, et al. Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis. Circulation. 2019;139(4):431-443. doi:10.1161/circulationaha.118.035831.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Sperry B.W., Quan D., Mauricio E., et al. EFFECT OF RNAI ON CARDIOMYOPATHY AND POLYNEUROPATHY OUTCOMES IN PATIENTS WITH V122I VARIANT HEREDITARY TRANSTHYRETIN-MEDIATED (HATTR OR ATTRV) AMYLOIDOSIS. Journal of the American College of Cardiology. 2023;81(8 Supplement):343. doi:10.1016/s0735-1097%2823%2900787-8.	Excluded: Exclude: Population not of interest (patients without ATTR-CM, aged <18 years)
Vest J, Solomon S, Adams D, et al. APOLLO, a phase 3 study of patisiran for the treatment of hereditary transthyretin amyloidosis (hATTR): 18-month safety and efficacy in subgroup with cardiac involvement. 2019;46:S20. doi:10.1017/cjn.2019.125.	Excluded: Exclude: Conference abstract published prior to 2022
Whelan C., Coelho T., Conceicao I., et al. Long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloid polyneuropathy with or without cardiomyopathy: Post hoc analysis of NEURO-TTR open-label extension. European Heart Journal. 2021;42(SUPPL 1):2745. doi:10.1093/eurheartj/ehab724.2745.	Excluded: Exclude: Conference abstract published prior to 2022
Witteles R, Sultan MB, Gundapaneni B, Garcia-Pavia P. Atrial fibrillation as a prognostic factor for all-cause mortality in patients with transthyretin amyloid cardiomyopathy. 2022;60:861. doi:10.1093/eurheartj/ehac544.861.	Excluded: Exclude: Outcomes not of interest
Yarlas A, Sikora Kessler A, Lovley A, Guthrie S, Pollock M, White MK. IMPACT OF INOTERSEN ON GENERIC HEALTH-RELATED QUALITY OF LIFE FOR PATIENTS WITH HATTR AMYLOIDOSIS: RESULTS FROM A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL. 2018;21:S354. doi:10.1016/j.jval.2018.09.2900.	Excluded: Exclude: Conference abstract published prior to 2022
Yarlas A, Sikora Kessler A, Lovley A, Guthrie S, Pollock M, White MK. ANALYSIS OF RESPONSES TO SF-36V2 ITEMS FOR PATIENTS WITH HATTR AMYLOIDOSIS: RESULTS FROM A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL. 2018;21:S354. doi:10.1016/j.jval.2018.09.2901.	Excluded: Exclude: Conference abstract published prior to 2022
Improvement in quality of life in patients with hereditary transthyretin amyloidosis with polyneuropathy and cardiomyopathy treated with inotersen in the phase 3 study NEURO-TTR. 2019;48(5):1135. doi:10.1016/j.hrtlng.2019.08.004.	Excluded: Exclude: Conference abstract published prior to 2022

APOLLO-B: a Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy). APOLLO-B: a Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy). 2019;	Excluded: Exclude: Publication type not of interest (narrative reviews, case reports, dissertations, letters, editorials, comments, notes, erratum, and trial protocols)
Efficacy of Tafamidis in Transthyretin Amyloid Cardiomyopathy in the ATTR-ACT Trial. 2019;48(5):470. doi:10.1016/j.hrtlng.2019.08.005.	Excluded: Exclude: Conference abstract published prior to 2022

Source: (81).

Local adaptation

The local adaptation of the SLR excluded the references presented in Table 69.

Table 69 List of excluded full-text references (local adaptation)

Citation	Reason for exclusion
MATHEW S MAURER, MARIANNA FONTANA, JOHN BERK, FINN GUSTAFSSON, MARCUS SIMOES, MARTHA GROGAN, FABIO FERNANDES, ROBERT L GOTTLIEB, MILOS KUBANEK, STEEN POULSEN, THIBAUD DAMY, IGOR DIEMBERGER, NOBUHIRO TAHARA, WENCHUNG YU, W.H. WILSON TANG, LAURA OBICI, ALEJANDRA GONZALEZ-DUARTE, YOSHIKI SEKIJIMA, MATTHEW T WHITE, SETH ARUM, PATRICK Y JAY, JOHN VEST, JULIAN D GILLMORE. Primary Results From Apollo-B, A Phase 3 Study Of Patisiran In Patients With Transthyretin-Mediated Amyloidosis With Cardiomyopathy	Intervention not of interest
Damy T, Shah Z, Drachman B, et al. Evaluation of disease progression in patients with ATTR amyloidosis with cardiomyopathy following treatment with patisiran: post-hoc analysis of the APOLLO-B study. European Heart Journal.	Intervention not of interest
Cappelli F, Kale P, Maurer M, et al. EXPLORATORY ANALYSES FROM APOLLO-B, A PHASE 3 STUDY OF PATISIRAN IN PATIENTS WITH ATTR AMYLOIDOSIS WITH CARDIOMYOPATHY. 2023;25:D181. doi:10.1093/eurheartjsupp/suad111.425.	Intervention not of interest
M.S. Maurer, P. Kale, M. Fontana, J.L. Berk, M. Grogan, F. Gustafsson, R.R. Hung, R.L. Gottlieb, T. Damy, A. González-Duarte, N. Sarswat, Y. Sekijima, N. Tahara, M.S. Taylor, M. Kubanek, E. Donal, T. Palecek, K. Tsujita, W.H.W. Tang, W.-C. Yu, L. Obici, M. Simões, F. Fernandes, S.H. Poulsen, I. Diemberger, F. Perfetto, S.D. Solomon, M. Di Carli, P. Badri, M.T. White, J. Chen, E. Yureneva, M.T. Sweetser, P.Y. Jay, P.P. Garg, J. Vest, and J.D. Gillmore, for the	Intervention not of interest

APOLLO-B Trial Investigators. Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis	
PARAG KALE, MATHEW S MAURER, MARIANNA FONTANA, MARTHA GROGAN, FABIO FERNANDES, TOMAS PALECEK, MARK S TAYLOR, REBECCA R HUNG, ALEJANDRA GONZALEZ-DUARTE, STEEN POULSEN,ERWAN DONAL, FEDERICO PERFETTO, KENICHI TSUJITA, WEN-CHUNG YU, NITASHA SARSWAT, MATTHEW T WHITE, SETH ARUM, PATRICK Y JAY, JOHN VEST, JULIAN GILLMORE. Exploratory Analyses From Apollo-B, A Phase 3 Study Of Patisiran In Patients With Attr Amyloidosis With Cardiomyopathy	Intervention not of interest
Longhi S, Maurer M, Fontana M, et al. PRIMARY RESULTS FROM APOLLO-B, A PHASE 3 STUDY OF PATISIRAN IN PATIENTS WITH TRANSTHYRETIN-MEDIATED AMYLOIDOSIS WITH CARDIOMYOPATHY. 2023;25:D28. doi:10.1093/eurheartjsupp/suad111.065.	Intervention not of interest
Noel R. Dasgupta, Stacy M. Rissing, Jessica Smith, Jeesun Jung & Merrill D. Benson (2020) Inotersen therapy of transthyretin amyloid cardiomyopathy, Amyloid, 27:1,52-58, DOI: 10.1080/13506129.2019.1685487	Intervention not of interest
Wixner, J. et al. Diflunisal treatment for hereditary transthyretin amyloidosis – the Swedish DFNS-02 trial. ISA 2022 Abstract #OP048	Intervention not of interest
Samuels, Leo. Coughlin, Sloan. Giblin, Gerard. Tolerability and side-effects of therapy in an open-label trial of inotersen for transthyretin amyloid cardiomyopathy (the INOCARD trial)	Intervention not of interest
COUGHLIN SLOAN M. BS1, SAMUELS LEO, BS1, GIBLIN GERARD T, Quality of Life in Patients with Transthyretin Amyloid Cardiomyopathy Treated with Inotersen.	Intervention not of interest
GERARD T. GIBLIN MBBCh1, CRYSTAL R. WALKER BS1, LEO C. SAMUELS,. Effect of inotersen on global longitudinal strain in transthyretin cardiac amyloidosis.	Intervention not of interest
GERARD T. GIBLIN MBBCh1, CRYSTAL R. WALKER BS1, LEO C. SAMUELS BS1. Inotersen treatment in transthyretin amyloid cardiomyopathy results in early and sustained serum transthyretin knockdown.	Intervention not of interest
Hoffman JE, Gundapaneni B, Sultan MB, Elliott P. Five-year Survival With Tafamidis In Patients With Transthyretin Amyloid Cardiomyopathy. Journal of Cardiac Failure. 2022 Apr 1;28(5):S102.	Outcomes not of interest
Miller AB, Januzzi JL, O'Neill BJ, Gundapaneni B, Patterson TA, Sultan MB, López-Sendón J. Causes of cardiovascular hospitalization and death in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin	Outcomes not of interest

Cardiomyopathy Clinical Trial [ATTR-ACT]). The American journal of cardiology. 2021 Jun 1;148:146-50.	
Nativi-Nicolau J, Judge DP, Hoffman JE, Gundapaneni B, Keohane D, Sultan MB, Grogan M. Natural history and progression of transthyretin amyloid cardiomyopathy: insights from ATTR-ACT. ESC Heart Failure. 2021 Oct;8(5):3875-84.	Outcomes not of interest
Li H, Rozenbaum M, Casey M, Sultan MB. Estimating the effect of tafamidis on cardiovascular-related hospitalization in NYHA class III patients with transthyretin amyloid cardiomyopathy in the presence of death. Cardiology. 2022 Oct 17;147(4):398-405.	Outcomes not of interest
Elliott P, Klein AL, Fernandes F, Gundapaneni B, Sultan MB, Shah SJ. Tafamidis Reduces The Decline In Longitudinal Strain And Stroke Volume In Patients With Transthyretin Amyloid Cardiomyopathy. Journal of Cardiac Failure. 2022 Apr 1;28(5):S102-3.	Outcomes not of interest
Sperry BW, Hanna MA, Nativi-Nicolau J, Maurer MS, Stewart M, Wyrwich K, Barsdorf A, Kapadia H, Floden L, Spertus JA. HEALTH STATUS IN PATIENTS WITH ATTR CARDIAC AMYLOIDOSIS RECEIVING TAFAMIDIS: RESPONDER ANALYSES FROM ATTR-ACT. Journal of the American College of Cardiology. 2022 Mar 8;79(9_Supplement):304-.	Outcomes not of interest
Hanna M, Damy T, Garcia-Pavia P, Judge DP, Merlini G, Maurer MS, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Witteles R. Efficacy and Safety of Tafamidis Doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). Journal of Cardiac Failure. 2019 Aug 1;25(8):S77-8.	Outcomes not of interest
Pavia PG, Sultan MB, Gundapaneni B, Sekijima Y, Perfetto F, Witteles R. EFFICACY OF TAFAMIDIS IN PATIENTS 80 YEARS AND OLDER WITH TRANSTHYRETIN AMYLOID CARDIOMYOPATHY IN ATTR-ACT. 2023;81(8):337. doi:10.1016/s0735-1097(23)00781-7.	Outcomes not of interest
Sperry B, Hanna M, Maurer M, et al. Association of Tafamidis With Health Status in Patients With ATTR Cardiac Amyloidosis: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. JAMA cardiology. 2023;8(3):275-280. doi:10.1001/jamacardio.2022.5251.	Outcomes not of interest
Rozenbaum M, Tran D, Bhambri R, Nativi-Nicolau J. Annual Cardiovascular-Related Hospitalization Days Avoided with Tafamidis in Patients with Transthyretin Amyloid Cardiomyopathy. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2022;22(4):445-450. doi:10.1007/s40256-022-00526-9.	Outcomes not of interest
Rapezzi C, Elliott P, Damy T, et al. Efficacy of Tafamidis in Patients With Hereditary and Wild-Type Transthyretin Amyloid	Outcomes not of interest

Cardiomyopathy: Further Analyses From ATTR-ACT. JACC. Heart failure. 2021;9(2):115-123. doi:10.1016/j.jchf.2020.09.011.	
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Sperry BW, Sultan MB, Gundapaneni B, Tai SS, Witteles R. EFFECT OF TAFAMIDIS ON RENAL FUNCTION IN PATIENTS WITH TRANSTHYRETIN AMYLOID CARDIOMYOPATHY IN ATTR-ACT. 2023;81(8):336. doi:10.1016/s0735-1097(23)00780-5.	Outcomes not of interest
Shah S, Fine N, Garcia-Pavia P, et al. Effect of Tafamidis on Cardiac Function in Patients With Transthyretin Amyloid Cardiomyopathy: A Post Hoc Analysis of the ATTR-ACT Randomized Clinical Trial. JAMA cardiology. 2023;doi:10.1001/jamacardio.2023.4147.	Outcomes not of interest
Grogan M., Sultan M., Gundapaneni B. Long-term tafamidis treatment reduces the decline in quality of life among patients. International Symposium of amyloidosis. 2022	Study design not of interest
Elliott P, Drachman B, Gottlieb S, et al. Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. Circulation. Heart failure. 2022;15(1):e008193. doi:10.1161/circheartfailure.120.008193.	Study design not of interest
Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. Improved survival with around 5 years of continuous tafamidis treatment among patients with NYHA class III transthyretin amyloid cardiomyopathy. 2022;24:98. doi:10.1002/ejhf.2569.	Study design not of interest
Garcia-Pavia P, Sultan M, Gundapaneni B, et al. Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study. JACC. Heart failure. 2023;doi:10.1016/j.jchf.2023.08.032.	Study design not of interest
Elliott P, Gundapaneni B, Sultan M, Ines M, Garcia-Pavia P. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. European journal of heart failure. 2023;doi:10.1002/ejhf.2974.	Study design not of interest
Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, Quyyumi AA, Aarts J, Falk RH. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. Circulation: Heart Failure. 2015 May;8(3):519-26.	Study design not of interest
Pfizer. Safety And Efficacy Evaluation Of Fx-1006a In Patients With V122i Or Wild-Type Transthyretin (TTR) Amyloid Cardiomyopathy. https://clinicaltrials.gov/show/NCT00935012	Study design not of interest

Masri, A. et al. Long-term safety and tolerability of acoramidis (AG10) in symptomatic transthyretin amyloid cardiomyopathy: Updated analysis from an ongoing phase 2 open-label extension study. ISA 2022 Abstract #OP011	Study design not of interest
Judge D, Heitner S, Falk R, et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. Journal of the American College of Cardiology. 2019;74(3):285-295. doi:10.1016/j.jacc.2019.03.012.	Study design not of interest

H.1.4 Quality assessment

The quality assessment was completed for the four RCTs (APOLLO-B (88), ATTR-ACT (51), ATTRibute-CM (90), and Study of AG10 (96)) using the Cochrane Risk of Bias 2 tool. It consists of several domains, each addressing different aspects of bias that may arise in the design, conduct, and reporting of RCTs. For each domain a rating of low, moderate, or high risk of bias was assessed by the reviewer to determine the reliability of RCT's results. The four included RCTs demonstrated a low risk of bias across all domains, resulting in an overall assessment of low risk of bias for all four trials (81).

H.1.5 Unpublished data

Not reported.

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

I.1 Health-related quality-of-life search

As mentioned in Appendix H, a systematic literature review (SLR) was conducted on the available literature on clinical efficacy, safety, quality of life, economic burden, and economic value of treatments in patients with wild-type or variant transthyretin amyloid cardiomyopathy (ATTR-CM) (81).

Searches were conducted independently for each scope topic (clinical, economic evaluations, costs and healthcare resource use, and utilities), with results of the literature search also being presented by scope topic. The clinical search included efficacy, safety and HRQoL outcomes in its inclusion criteria. These are the only relevant endpoints presented in this application and, therefore, the methods and results for the other scope topics (economic evaluations, costs and healthcare resource use, and utilities) were not presented in this application. Utilities were not relevant as the feasibility assessment conducted before the MAIC deemed the comparison not possible due to the fact that the ATTR-ACT trial only reported EQ-5D data for the pooled tafamidis dose. Please refer to Appendix H for the methods and results of the clinical search that included HRQoL data (KCCQ-OS data) included in this application.

Table 70 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Not applicable			

Abbreviations:

Table 71 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Not applicable			

Table 72 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Not applicable				

I.1.1 Search strategies

Not applicable.

Table 73 Search strategy for [name of database]

No.	Query	Results
#1	Not applicable	88244

Literature search results included in the model/analysis:

Not applicable.

I.1.2 Quality assessment and generalizability of estimates

Not applicable.

I.1.3 Unpublished data

Not applicable.

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

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

J.1.1 Example: Systematic search for […]

Not applicable.

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Not applicable			

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

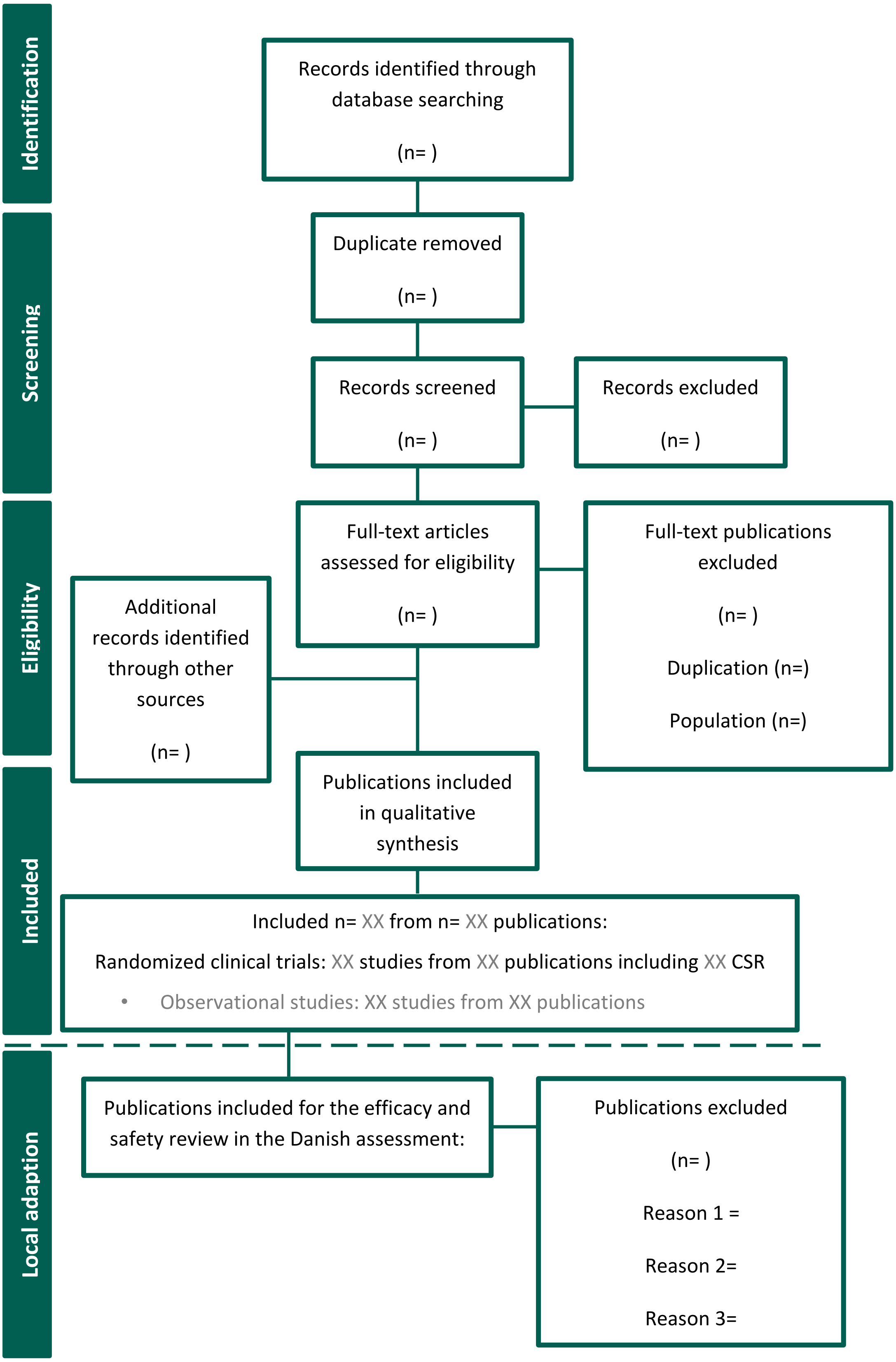
Not applicable.

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
Not aplicable			

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.


Identification
Screening
Eligibility
Included
Local adaption
Records identified through database searching
(n=)
Duplicate removed
(n=)
Records screened
(n=)
Records excluded
(n=)
Full-text articles assessed for eligibility
(n=)
Full-text publications excluded
(n=)
Duplication (n=)
Population (n=)
Additional records identified through other sources
(n=)
Publications included in qualitative synthesis
Included n= XX from n= XX publications:
Randomized clinical trials: XX studies from XX publications including XX CSR
• Observational studies: XX studies from XX publications
Publications included for the efficacy and safety review in the Danish assessment:
Publications excluded
(n=)
Reason 1 =
Reason 2=
Reason 3=

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