Direktoratet for
medisinske produkter

Akoramidis (Beyonttra)

Til behandling av villtype eller variant (arvelig) transtyretin amyloidose hos voksne pasienter med kardiomyopati (ATTR-CM).

ID2024_071

Metodevurdering av enkeltlegemiddel finansiert i spesialisthelsetjenesten

16.06.2025

Forord

De regionale helseforetakene har ansvar for det nasjonale systemet for innføring av nye metoder i spesialisthelsetjenesten, Nye metoder. Prinsippene for prioritering i helsetjenesten er angitt i stortingsmelding 34 (2015-2016), "Verdier i pasientens helsetjeneste — Melding om prioritering", vedtatt av Stortinget i 2016. Nye metoder skal bidra til at legemidler som er aktuelle å innføre i spesialisthelsetjenesten blir vurdert på en systematisk måte, og dermed bidra til forsvarlig bruk av ressursene i helsetjenestene. Systemet for Nye metoder har vært lovfestet siden 2019 og er nærmere beskrevet på Nye metoder sine hjemmesider, www.nyemetoder.no.

Før et nytt legemiddel kan tas i bruk i spesialisthelsetjenesten, må det foreligge en beslutning om innføring av Beslutningsforum. Dette er et beslutningsorgan satt sammen av direktørene for de regionale helseforetakene. Beslutningsforum tar den endelige avgjørelsen om innføring av nye legemidler i spesialisthelsetjenesten etter en samlet vurdering av de tre prioriteringskriteriene nytte, ressursbruk og alvorlighet. Direktoratet for medisinske produkter (DMP) sin rolle er å gjennomføre metodevurderinger som belyser prioriteringskriteriene ved den aktuelle bruken. Metodevurderingen inngår som del av beslutningsgrunnlaget til Beslutningsforum.

Nytten måles ved hvor mange gode leveår den nye behandlingen i gjennomsnitt gir for pasienter i den aktuelle pasientgruppen sammenliknet med relevant behandlingspraksis. Med et godt leveår menes et år med "perfekt" helse, dvs. helt uten sykdom/plager, på fagspråket definert som et kvalitetsjustert leveår (1 QALY). Dette er en standardisert beregningsmetode som gjør det mulig å sammenligne nytten av ulike behandlinger som brukes mot ulike sykdommer.

Ressursbruk beregnes med utgangspunkt i gjennomsnittlig legemiddelkostnad og øvrig ressursbruk i helse- og omsorgstjenesten, sammenliknet med relevant behandlingspraksis.

Alvorlighet måles ved hvor mange gode leveår pasienter i den aktuelle gruppen i gjennomsnitt taper ved fravær av behandlingen som vurderes.

Legemidlets rettighetshaver har ansvar for å sende inn nødvendig dokumentasjon til DMP før metodevurdering, i henhold til bestilling fra Bestillerforum. DMP kan gi veiledning til legemiddelfirmaet.

DMP vurderer det innsendte datagrunnlaget for kliniske utfall, alvorlighet, angitt ressursbruk, forutsetninger for analysen og de presenterte analyseresultater. DMP kan ved behov innhente tilleggsopplysninger hos legemidlets rettighetsinnehaver, det kliniske fagmiljøet og brukere, og kan foreta egne beregninger av kostnader og kostnadseffektivitet. DMP vurderer ikke forholdet mellom effekt og sikkerhet (nytte-risiko-balansen). Dette utredes av den europeiske legemiddelmyndigheten (EMA) under prosedyren for markedsføringstillatelse.

For å sikre at metodevurderingen er dekkende og relevant for norske forhold, samt å avklare sentrale forutsetninger lagt til grunn av legemidlets rettighetshaver, er det viktig med involvering av medisinske fageksperter. De regionale helseforetakene (RHF) rekrutterer medisinske fageksperter innenfor relevant sykdomsområde som kan bistå DMP i oppdrag om metodevurdering. Både fageksperten selv, helseforetakene og DMP må ta stilling til om fageksperten anses å være habil til å delta i det aktuelle oppdraget. Fagekspertene fungerer som rådgivere i arbeidet, og involvering skjer gjennom arbeidsmøter og/eller skriftlig kommunikasjon mellom DMP og rekrutterte medisinske fageksperter underveis i utredningen. Fagekspertene får også mulighet til å kommentere på rapporten generelt, men har ikke fagfellefunksjon. Hensikten er at fagekspertene kontrollerer at DMP har oppfattet og brukt deres bidrag hensiktsmessig. DMP er selv ansvarlig for innholdet i rapporten. Fageksperters rolle i metodevurderinger i systemet for Nye metoder er nærmere beskrevet på DMPs hjemmesider (www.dmp.no).

DMP har ikke beslutningsmyndighet i systemet for Nye metoder, men metodevurderingsrapportene inngår i beslutningsgrunnlaget til Beslutningsforum. Sykehusinnkjøp HF forhandler pris på nye legemidler i Nye metoder. Prisen for et legemiddel påvirker kostnaden for behandling, og dermed kostnaden per kvalitetsjusterte leveår. Hvor mye samfunnet er villig til å betale for et kvalitetsjustert leveår henger sammen med alvorlighetsgraden til sykdommen.

Noe av informasjonen i DMPs rapporter kan være taushetsbelagt etter ønske fra legemidlets rettighetshaver. DMP vurderer legemiddelfirmaets ønsker om unntak fra offentlighet og tar stilling til om opplysningene er taushetsbelagte (jf. forvaltningsloven § 13 første ledd, se her for retningslinjer). Alle metodevurderingsrapportene publiseres, og er offentlig tilgjengelig på DMPs hjemmesider (www.dmp.no).

Sammendrag

Metode

Metodevurdering av legemiddelet akoramidis (Beyonttra). Direktoratet for medisinske produkter (DMP) har vurdert prioriteringskriteriene alvorlighet, nytte og ressursbruk, samt usikkerhet i dokumentasjonen. Det europeiske legemiddelbyrået (EMA) har vurdert at akoramidis har en nytte som overstiger risikoen ved bruk, og Europakommisjonen har utstedt markedsføringstillatelse. For metodevurderingen er det nytte og kostnader av den nye metoden sammenlignet med dagens behandlingsalternativ i norsk klinisk praksis som er relevant.

DMPs vurdering tar utgangspunkt i dokumentasjon innsendt av Bayer AG på vegne av BridgeBio Europe B.V. De regionale helseforetakene har oppnevnt fire medisinske fageksperter til oppdraget om metodevurdering. Disse har bistått DMP med avklaringer rundt behandling for pasientgruppen i norsk klinisk praksis, forventet plassering av akoramidis i behandlingsalgoritmen, overførbarhet av studiedata til norsk pasientpopulasjon, og forventede effekter av behandling.

Oversikt over metodevurderingen	
Bestilling	ID2024_071 Akoramidis (Beyonttra) til behandling av villtype eller variant (arvelig) transtyretin amyloidose hos voksne pasienter med kardiomyopati. En metodevurdering med en helseøkonomisk analyse (en indirekte sammenligning av relativ effekt og sikkerhet versus tafamidis) og en sammenligning av legemiddelkostnader basert på innsendt dokumentasjon fra leverandør gjennomføres av Direktoratet for medisinske produkter (DMP). Et tilhørende prisnotat utarbeides av Sykehusinnkjøp HF.
Legemiddelfirma	Bayer, på vegne av BridgeBio
Preparat	Beyonttra
Virkestoff	Akoramidis
ATC-kode	C01EB25
Aktuell indikasjon	Akoramidis er indisert til behandling av villtype eller variant transtyretinamyloidose hos voksne pasienter med kardiomyopati (ATTR-CM).
Virkningsmekanisme	Ved økende alder eller genetiske mutasjoner kan proteinet transtyretin folde seg feil og gi ustabile proteiner som kan danne amyloidavleiringer i hjertet. Akoramidis stabiliserer proteinet transtyretin og forhindrer amyloidavleiringer, slik at hjertet kan opprettholde sin normale funksjon.
Dosering	712 mg (to tabletter, 356 mg) oralt, to ganger daglig (total daglig dose er 1 424 mg). Behandlingen er langvarig.
Helseøkonomisk analyse vurdert av DMP	Ja ☒ Type: Kostnadsminimeringsanalyse Nei ☐
Rabatterte legemiddelpriser	Det foreligger forhandlede rabatterte legemiddelpriser på komparator tafamidis. Resultater basert på konfidensielle priser vil fremkomme i et separat dokument som oversendes til aktører med tjenstlig behov for denne informasjonen.

Sykdom

Transtyretin amyloid kardiomyopati	
Om sykdommen	Ved amyloidavleiring i hjertet blir hjerteveggene tykkere samtidig som hjertekammervolumene reduseres. Dette reduserer hjertets evne til å pumpe blod. Det oppstår en kombinert høyresidig og venstresidig hjertesvikt, som gjør at blodet hoper seg opp i sirkulasjonen. Tilstanden gir perifere ødemer, venestuvning, slapphet og tretthet, tung pust ved aktivitet og etter hvert også ved hvile.
Behandling i norsk klinisk praksis	Tafamidis er innført med visse kriterier i Nye Metoder til behandling av ATTR-CM med hjertesvikt i NYHA klasse I og II
Pasientgrunnlag i Norge	Basert på tall fra Legemiddelregisteret ble 473 pasienter behandlet med tafamidis i 2024.

Vurdering av prioriteringskriteriene, budsjettkonsekvenser og usikkerhet ved innføring av den nye metoden

DMPs vurdering av nytte:
Effekt og sikkerhet av akoramidis sammenlignet med placebo er undersøkt i ATTRibute-CM, en randomisert, dobbeltblindet fase 3-studie som inkluderte 632 pasienter med ATTR-CM. I norsk klinisk praksis er tafamidis relevant komparator, men det finnes ingen studier som direkte sammenligner disse to legemidlene ved aktuell indikasjon.

DMP har vurdert en indirekte sammenligning av akoramidis (ATTRibute-CM studien) og tafamidis (ATTR-ACT studien). Det er utført statistiske sammenligninger for å etablere relativ effekt på utfallene totaloverlevelse, kardiovaskulærrelaterte sykehusinnleggelser, gangfunksjon (6-minutters gangtest) og livskvalitet (KCCQ-OS). Det er også utført en indirekte sammenligning av uønskede hendelser/sikkerhet. Analysene omfattet en rekke scenarier med justering for ulike populasjonsforskjeller. Basert på resultatene fra disse analysene vurderer DMP at akoramidis og tafamidis sannsynligvis ikke skiller seg vesentlig fra hverandre når det gjelder effekt og sikkerhet.

En undergruppe i ATTRibute-CM studien fikk tafamidis samtidig med akoramidis. Kombinasjonsbehandling med tafamidis og akoramidis ga ingen ytterligere økning av serum TTR, som er et mål for TTR-stabilisering, sammenlignet med akoramidis alene. Kombinasjonsbehandling med tafamidis og akoramidis ga heller ingen ytterligere reduksjon av NT-proBNT, en biomarkør for hjertesvikt, sammenlignet med akoramidis alene. DMP vurderer derfor at det ikke er vist noen mernytte av kombinasjonsbehandling i ATTRibute-CM studien.

DMPs vurdering av ressursbruk:
Legemiddelkostnaden for en måneds behandling med akoramidis er om lag NOK 100 000, basert på maksimal AUP uten mva. I kostnadsminimeringsanalysen er kun legemiddelkostnader inkludert ettersom andre kostnader vurderes å være de samme som for komparator tafamidis. Beregningene tar utgangspunkt i anbefalt dosering i preparatomtalene. Gjennomsnittlig totalkostnad for et års behandling med akoramidis er ca. NOK 1,2 millioner (maksimal AUP uten mva) per pasient. Dette er ca NOK 40 000 mindre per pasient per år sammenlignet med kostnader for behandling med tafamidis. Det foreligger konfidensielle, rabatterte priser for tafamidis.

DMPs vurdering av alvorlighet:
Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. I metodevurderingen av tafamidis til behandling av ATTR-CM estimerte DMP at denne

populasjonen behandlet med datidens standardbehandling hadde et absolutt prognosetap (APT) på ca. 8-9 QALY.

DMPs vurdering av budsjettvirkninger:

DMP har ikke beregnet budsjettvirkninger ettersom dette er en kostnadminimeringsanalyse. Gitt at prisnivå ved innføring vil være likt mellom tafamidis og akoramidis, estimeres det ingen økte budsjettvirkninger dersom akoramidis innføres.

DMPs vurdering av usikkerhet:

Resultater fra indirekte sammenligninger har lavere evidens og er generelt heftet med mer usikkerhet enn når intervensjon og komparator sammenlignes direkte i randomiserte studier. Slike analyser gir som regel brede konfidensintervaller, og forskjeller mellom studiepopulasjonene kan påvirke resultatene. I denne saken har Bayer levert flere supplerende analyser som justerer for ulike effektmodifiserende faktorer. Analysene peker generelt i retning av det ikke er grunn til å anta at akoramidis og tafamidis har vesentlig forskjellig effekt og sikkerhet. Dette støttes også av de medisinske fagekspertene. I tillegg har legemidlene lignende virkningsmekanisme. Samlet vurderer DMP at saken er godt opplyst.

Det er ingen pågående studier som direkte sammenligner effekt av akoramidis versus tafamidis. DMP forventer derfor ikke at det vil tilkomme ytterligere dokumentasjon som kan belyse saken nærmere.

Logg

Tidslogg for oppdraget	
Beskrivelse	**Dato/antall dager**
Tidspunkt for MT for <legemiddelet/indikasjonsutvidelsen>	10-02-2025
Oppdrag gitt av Bestillerforum RHF	20-01-2025
Dokumentasjon mottatt hos DMP	03-03-2025
Medisinske fageksperter rekruttert til saken	25-03-2025
Saken tildelt saksutreder(e)	12-03-2025
Medisinske fageksperter involvert i saken fra og med	28-03-2025
Rapport ferdigstilt	16-06-2025
Total tid hos DMP[1]	105 dager
Herunder:	
Tid i påvente av opplysninger fra legemiddelfirma	36 dager
Saksbehandlingstid hos DMP[2]	**69 dager**
Herunder[3]:	
Tid i påvente av rekruttering av medisinske fageksperter	21 dager
Tid i kø i påvente av tildeling til saksutreder(e)	9 dager

[1] Tid fra mottatt dokumentasjon til ferdigstilling av rapport.
[2] Tid fra mottatt dokumentasjon til ferdigstilling, fratrukket tid i påvente av opplysninger fra legemiddelfirma
[3] Tid i påvente av rekruttering av medisinske fageksperter og tid i kø i påvente av tildeling til saksutreder(e) kan overlappe.

Medisinske fageksperter rekruttert til oppdraget	
Navn	**Tilknytning**
Håvard Dalen	St. Olavs hospital og NTNU
Håvard Ravnestad	Oslo Universitetssykehus
Jørg Saberniak	Akershus universitetssykehus
Einar Skulstad Davidsen	Haukeland universitetssykehus
Medisinske fageksperter har bidratt med avklaringer av sentrale forutsetninger i metodevurderingen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). DMP er ansvarlig for rapportens innhold. Medisinske fageksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten	

DMP		
Navn	**Rolle i metodevurderingen**	**Stillingstittel**
Christine Sommer-Jacobsen	Utredningsleder	Seniorrådgiver
Ania Urbaniak	Saksutreder	Seniorrådgiver
Reidun Husteli	Saksveileder/kvalitetssikrer	Seniorrådgiver
Kirsti Hjelme	Kvalitetssikrer	Seniorrådgiver
Anette Grøvan	Har godkjent endelig rapport	Enhetsleder

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Abbreviations

Forkortelse	Betydning
6MWT/D	6-minute walk test/distance
ACM	All-cause mortality
ATTR-CM	Transthyretin amyloid cardiomyopathy
AUP	Apotekenes utsalgspris
BSC	Best supportive care
CI	Confidence interval
CV	Cardiovascular
CVH	Cardiovascular hospitalizations
EMA	European Medicines Agency
HR	Hazard ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire overall summary
MAIC	Matching-adjusted indirect comparison
NOMA	Norwegian Medical Products Agency
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA classification	New York Heart Association classification
SGLT2	Sodium-glucose linked transporter 2
STA	Single technology assessment
TTR	transthyretin
VAT	Value-added tax

Background

1.1 Overview of the assignment

In the single technology assessment (STA), the criteria of prioritization – severity, utility and resource use (cost-effectiveness) are evaluated – along with uncertainty in the documentation and budgetary consequences. The European Medicines Agency (EMA) has concluded that acoramidis has a benefit that outweighs the risks of its use, and the European Commission has issued marketing authorization. For the STA, the relative effect and additional cost of the new method compared to current treatment options in Norwegian clinical practice are relevant. Norwegian Medical Products Agency's (NOMA) STA is based on documentation submitted by Bayer AG on behalf of BridgeBio Europe B.V., later referred to as Bayer.

1.1.1 Intervention

Table 1. The intervention to which this single technology assessment applies.

Acoramidis (Beyonttra)	
Indication relevant to the STA	For the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
Other indications with approval	None.
Mechanism of action	Transthyretin amyloid cardiomyopathy (ATTR-CM) results from misfolding and deposition of transthyretin (TTR) in the heart. Acoramidis is a high-affinity stabilizer of TTR. Acoramidis mimics a protective genetic variant, which binds and stabilizes reactive forms of TTR protein to slow the amyloidogenic process that leads to ATTR-CM.
Posology	The recommended dose of acoramidis is 712 mg (two tablets, 356 mg) orally, twice daily, totaling a daily dose of 1424 mg. Long-term treatment.

1.1.2 Scope of the assignment

The table below outlines the order from Bestillerforum and scope of the STA. This method involves a new active substance that received marketing authorization on February 10, 2025. The order complies with the approved indication.

Table 2. Scope of the single technology assessment.

Scope of the assignment	
Order	ID2024_071: En metodevurdering med en helseøkonomisk analyse (en indirekte sammenligning av relativ effekt og sikkerhet versus tafamidis) og en sammenligning av legemiddelkostnader basert på innsendt dokumentasjon fra leverandør gjennomføres av Direktoratet for medisinske produkter (DMP). Et tilhørende prisnotat utarbeides av Sykehusinnkjøp HF.
Analysis	Cost-minimization
PICO	
	Description
Population	Adult ATTR-CM patients, variant and wild-type (overall population). Additional subgroup analyses are presented for patients in NYHA class I/II.
Intervention	Acoramidis
Comparator	Tafamidis
Outcomes	ACM, CVH, 6MWT, KCCQ-OS, safety, yearly treatment costs

ACM = all-cause mortality, CVH = cardiovascular hospitalizations, 6MWT = 6 minute walking test, KCCQ-OS = Kansas city cardiomyopathy questionnaire – overall summary.

There are no studies that directly compare the efficacy and safety of acoramidis vs. tafamidis, and this needs to be assessed in an indirect treatment comparison (ITC). Bayer, on behalf of BridgeBio, has provided ITCs in the form of anchored Bucher and MAIC analyses comparing acoramidis and tafamidis, based on results from the two randomized, placebo-controlled, double-blind, multi-center studies ATTRibute-CM of acoramidis (1) and ATTR-ACT of tafamidis (2). Bayer, on behalf of BridgeBio, has provided a cost-minimization analysis of acoramidis compared to tafamidis for the treatment of patients with ATTR-CM.

1.2 Cardiac amyloidosis with transthyretin deposition

Cardiac amyloidosis is a disorder caused by amyloid fibril deposition in the extracellular space of the heart. The amyloid fibril deposition gives cardiomyopathy, a disorder of the heart muscle. Transthyretin (TTR) is one of several proteins that can deposit in the heart, causing cardiac amyloidosis, specifically ATTR cardiomyopathy (ATTR-CM) (3). In ATTR-CM, TTR is primarily deposited in the heart but can also be found in smaller amounts in organs such as the lungs, kidneys, liver, and spleen. ATTR-CM is relatively rare in young persons, but the incidence increases with age (4).

ATTR-CM can present with cardiac signs or symptoms or may be diagnosed as the result of screening in patients who manifest extracardiac signs of amyloidosis (5). ATTR-CM often causes few and nonspecific symptoms, making it difficult to diagnose. At the time of diagnosis, dyspnea with diastolic heart failure is a common symptom, while arrhythmia and edema is less common (4). Atrial fibrillation, and carpal tunnel syndrome are common findings 5-10 years before the cardiac diagnosis (4).

ATTR-CM can be hereditary, where a gene mutation causes misfolding of ATTR, or non-hereditary, known as wild-type, where TTR becomes unstable and starts to misfold with increasing age. Symptomatic, wild-type ATTR-CM is most commonly seen in men (4).

The prevalence of hereditary ATTR-CM, also known as variant ATTR-CM, in Norway is not known, but there are individual cases of hereditary ATTR amyloidosis in several regions of Norway. All these patients are of foreign origin, and no unique "Norwegian" founder mutation has been identified so far. It can be difficult to distinguish wild-type from variant when ATTR presents at an older age (4).

Heart failure and NYHA classification

Heart failure means that the heart is unable to properly pump blood around the body. It usually happens because the heart has become too weak or stiff (6).

The severity of heart failure is divided into four different NYHA classes according to the New York Heart Association (NYHA) (7):

- NYHA I: Heart failure without symptoms
- NYHA II: Heart failure symptoms (dyspnea, tachycardia, fatigue) only during significant physical exertion, such as brisk walking uphill. The patient can walk 2–3 flights of stairs continuously.
- NYHA III: Heart failure symptoms during light to moderate physical exertion, such as daily activities, slow walking on flat ground, or walking up one flight of stairs.
- NYHA IV: Symptoms at rest or with minimal activity, such as personal care.

NT-proBNP

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is a diagnostic marker for heart failure (8). High levels indicate increased intracardial pressure, usually due to heart failure. Elevated levels are also seen in cardiomyopathy. NT-proBNP increases proportionally with NYHA classes (8).

eGFR
Estimated glomerular filtration rate (eGFR) is a diagnostic marker for kidney function (9). Heart failure can lead to reduced blood flow to the kidneys and impaired kidney function (10).

Diagnosis of ATTR-CM
Cardiac ATTR due to transthyretin deposition is likely underdiagnosed because non-invasive diagnostic methods were not available until recently. The introduction of the non-invasive bone tracer cardiac scintigraphy for amyloidosis has largely replaced the need for invasive heart biopsy in diagnosis of ATTR-CM. Due to available treatment options for transthyretin amyloidosis, such as tafamidis, screening for the condition at suspicion is more widespread today (3).

1.3 Severity and absolute shortfall

The benefit and cost criteria should be evaluated against the severity of the condition. Severity influences whether the costs are considered reasonable in relation to the benefits of the treatment. Higher severity justifies greater resource use compared to lower severity.

ATTR-CM is a severe condition with increased mortality and reduced quality of life, compared to age-matched controls. In the STA of tafamidis in ATTR-CM, absolute shortfall was estimated to be 8-9 QALYs for patients treated with the standard of care at that time(11).

1.4 Treatment of ATTR-CM in Norwegian Clinical Practice

According to medical experts recruited by the regional health authorities, they adhere to the Norwegian guideline for diagnostics and treatment of amyloidosis (4) in combination with the European Society of Cardiology (ESC) 2021 guideline for diagnosis and treatment of acute and chronic heart failure (12), and 2023 guidelines for Cardiomyopathies (13).

For ATTR-CM, the treatment goal is to manage (14):

- amyloidosis (tafamidis to prevent amyloidosis)
- heart failure (although some of the typical treatments for heart failure are not very effective or well documented (12)).
- arrhythmias, ischemia, and valve disorders

Liver transplant could be necessary in some patients with hereditary ATTR to reduce the amount of unstable TTR which is produced in the liver.

According to the recruited medical experts, pharmacological treatment of ATTR-CM has not changed much the last decade, apart from the fact that tafamidis is now available. Standard heart failure treatment is largely the same now as it was ten years ago, but sodium-glucose linked transport protein 2 (SGLT2) inhibitors have been increasingly added the last four years (since around 2021 for heart failure with reduced ejection fraction, and 2024 for heart failure with preserved ejection fraction). SGLT2 inhibitors represent the most notable change in supportive treatment and may potentially influence patient prognosis. However, it is not yet known whether, or to what extent, treatment with SGLT2 inhibitors impacts mortality in patients with ATTR-CM.

The recruited medical experts explain that in recent years there has been an increased ability to diagnose some of these patients earlier. The earlier diagnosis is partly due to greater awareness of the diagnosis and stronger incentives to identify this patient group now that ATTR-CM-specific treatment options are available. At the same time, non-invasive methods (such as scintigraphy and MRI) have partially replaced more invasive methods (like biopsies).

Another relevant change in Norwegian clinical practice, according to the medical experts, is that regional care in some areas is now organized into dedicated cardiomyopathy or amyloidosis outpatient clinics, leading to more specialized treatment.

Management of amyloidosis
Tafamidis (Vyndaqel) was introduced for treatment of wild-type or variant ATTR-CM in Norway as of July 15th 2022 (15), with the following criteria for treatment initiation and discontinuation:

- Treatment initiation can only be done by a cardiologist experienced in treating transthyretin amyloidosis (ATTR), employed at a university hospital or other healthcare institution with a cardiology unit competent in treating this patient group.
- The patient must have a definitive diagnosis of ATTR cardiomyopathy, usually with nuclear medicine-confirmed amyloid in the myocardium (meaning diagnosed with bone tracer cardiac scintigraphy). The patient should be in NYHA class I or II at the start of treatment.
- The patient should have an expected remaining life span significantly over 18 months.
- If progression to persistent (at least 6 months) NYHA class III occurs, the decision to continue treatment should be made in consultation with a cardiologist experienced in treating ATTR, employed at a university hospital or other healthcare institution with a cardiology unit competent in treating this patient group.
- If rapid progression to persistent NYHA class III occurs within 6 months after initiating treatment, the treatment should be discontinued.

1.5 Expected Position of Acoramidis in the Treatment Algorithm

Acoramidis' mechanism of action is similar to that of tafamidis, both drugs stabilize the tetrameric TTR(16, 17). Marketing authorizations for acoramidis and tafamidis include the same patient populations, the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

According to medical experts, there is reason to believe that the treatments are equivalent in terms of efficacy and safety. The same patients are thus eligible for both medications.

Concomitant use of acoramidis and tafamidis did not further increase serum TTR beyond what is achieved with acoramidis alone in the ATTRibute-CM study. According to the medical experts, concomitant use of acoramidis and tafamidis is not considered relevant due to the lack of evidence.

NOMA's conclusion about comparator
Tafamidis is the relevant comparator in Norwegian clinical practice. If introduced, acoramidis will be used in the treatment of the same patient population as tafamidis. i.e. patients with NYHA class I or II at the start of treatment.

2. Clinical evidence base

2.1 Identification of relevant clinical trials

Bayer has conducted systematic literature searches in relevant databases November 23, 2023. The searches were updated November 1st, 2024, complying with NOMAs guidelines for STAs that searches must be no older than 6 months at submission. The search strategy, search results, and study selection are sufficiently documented. See appendix 1 for the evaluation of the systematic literature search.

NOMA's conclusion on submitted literature search
DMP considers the literature search to be sufficiently documented and relevant for the assessment.

2.2 Overview of relevant, submitted trials

Table 3. Overview of submitted studies of acoramidis relevant to the single technology assessment.

ATTRibute-CM (acoramidis)	
Study ID (NCT number)	ATTRibute-CM (NCT03860935)
Study design	30-month, randomized, double-blind, placebo-controlled study (18)
Study location(s)	Locations in Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Greece, Ireland, Israel, Italy, Netherlands, New Zealand, Poland, Portugal, South Korea, Spain, United Kingdom, and the United States of America (19)
Population	Adult patients with ATTR-CM (wild-type or variant), n=632 Inclusion criteria: • Adults aged ≥18 to ≤90 years • NYHA Class I to III symptoms • Clinical HF with ≥1 previous hospitalization for HF or clinical evidence for HF • 6MWT ≥150 meters • NT-proBNP ≥300 to <8500 pg/mL • LV wall thickness ≥12 mm Exclusion criteria: • eGFR<15 mL/min/1.73 m^2 for the intention-to-treat population • Heart transplantation likely within a year of screening • AL amyloidosis • Abnormal liver function tests • Prior treatment with tafamidis • Marketed drug products lacking a labelled indication for ATTR-CM (e.g., diflunisal or doxycycline), or natural products or derivatives used as unproven therapies for ATTR-CM within 14 days prior to dosing (20) Stratification factors (patients were stratified at randomization): • TTR genotype (wild-type vs. variant) • NT-proBNP levels • eGFR

Intervention	Acoramidis hydrochloride 800 mg twice daily (equivalent to acoramidis 712 mg twice daily) + BSC (n=421) (19)
Comparator	Placebo + BSC (n=211) (19)
Primary endpoint	Hierarchical analysis over a 30-month period of: • ACM • Cumulative frequency of CV-related hospitalizations • NT-proBNP: change from baseline • 6MWD: change from baseline
Important secondary endpoint(s)	• 6MWD: change from baseline to Month 30 • KCCQ-OS score: change from baseline to Month 30 • Serum TTR: change from baseline to Month 30 • ACM: by Month 30
Observation time	Efficacy and safety outcome assessments were performed on Day 1, Day 28, Month 3, and repeated every 3 months until Month 30. Additionally, there were monthly telephone sessions to assess safety.
Data cuts	No formal interim analysis was planned. Predefined assessments were conducted after study participants had been on treatment for 12 months and for 30 months (21). Data cut-off: 06/07/2023 (20)
Was the study part of the EMA MA approval process relevant for this STA?	☒ Yes ☐ No

Abbreviations: 6MWT = Six-minute Walk test; 6MWD = Six-minute walk distance; ACM = All-cause mortality; ATTR-CM = transthyretin amyloid cardiomyopathy; CFB = change from baseline; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; HF = heart failure; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score; LV = left ventricular; MA = Market authorisation; NCT = national clinical trial; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; STA = single technology assessments; TTR = transthyretin
Source: (18-20, 22-25)

Relevant ongoing studies

The ATTRibute-CM open-label extension study (OLE) (NCT04988386; AG10-304) aims to evaluate the long-term safety and tolerability of acoramidis in patients with symptomatic ATTR-CM who completed the phase III ATTRibute-CM trial for 60 months or study completion.

NOMA's assessment

ATTRibute-CM forms the basis for the marketing authorization of acoramidis and is a randomized placebo-controlled phase 3 study assessed by EMA. As tafamidis (+ best supportive care, BSC) is the relevant comparator for Norwegian clinical practice, while placebo + BSC was comparator in ATTRibute-CM, it was necessary to perform an evidence synthesis to inform relative efficacy and safety versus the relevant comparator.

Ideally, an anchored ITC should be performed, as this minimizes the risk of bias. The OLE study has a longer follow-up period than the ATTRibute-CM study, providing supplementary data. However, the OLE study is not controlled and therefore unsuitable for an anchored indirect comparison of outcomes. NOMA concludes that, between the two studies, only the ATTRibute-CM study is appropriate for an anchored comparison.

2.3 Evidence synthesis to establish relative effect

The SLR identified the ATTR-ACT trial (tafamidis) as relevant for an ITC. Bayer has performed an ITC of ATTRibute-CM and ATTR-ACT (described in table 5).

Bayer has delivered an ITC of acoramidis vs. tafamidis for both the ITT population and for the NYHA I/II subgroup that is eligible for tafamidis in the Norwegian clinical practice.

Tafamidis was in 2022 introduced in Norway for patients with ATTR-CM with heart failure in NYHA I/II due to a lack of effect of tafamidis versus placebo in NYHA class III. According to EMA, subgroup analysis showed no benefit of acoramidis for patients within NYHA class III for primary or secondary endpoints (26).

The recruited medical experts state that the ATTRibute-CM study was not sufficiently powered to conclude on whether efficacy in patients with heart failure in NYHA class III differed from the study population as a whole.

In this cost-minimization analysis of acoramidis, NOMA's evaluation will focus mainly on the results from the ITC in the NYHA I/II subgroup and use the ITC in the ITT population as support when needed.

Table 4. PICO of the evidence synthesis.

Population	• Adult ATTR-CM variant and wild-type, with a subgroup analysis for the NYHA class I and II population • Efficacy analysis was based on the intention-to-treat (ITT) population, which included all randomised patients who received at least one dose of study medication and had at least one post baseline efficacy evaluation and excluded patients with eGFR <15 mL/min/1.73 m^2 at screening. • Hypothetical scenario with censoring of concomitant tafamidis use after 12 months • For safety, all analyses were based on the safety population, which included all patients who received at least one dose of study medication.
Intervention	• Acoramidis[a]
Comparator	• Tafamidis[a]
Outcomes	• All-cause mortality (HR [95% CI]) over 30 months • Cumulative frequency of cardiovascular-related hospitalisation (RRR [95% CI]) over 30 months • Change from baseline in distance walked during the 6MWT (LS mean difference [95%CI]) over 30 and 12 months • Change from baseline in the KCCQ-OS (LS mean difference [95%CI]) over 30 and 12 months • Safety
Study design	• Matching-adjusted indirect comparison (efficacy) • Bucher (safety)

[a] In the MAIC, 800 mg of acoramidis hydrochloride twice daily (equivalent to acoramidis 712 mg twice daily) was compared with 80 mg tafamidis meglumine once daily (equivalent to 61 mg tafamidis once daily).
Abbreviations: ATTR-CM = Transthyretin amyloid cardiomyopathy; CI = confidence interval; eGFR = estimated glomerular filtration rate; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score; HR = hazard ratio; LS = Least square; MAIC = Matching-adjusted indirect comparison; PICO = Population, Intervention, Comparator and Outcome; RRR = relative risk ratio

Table 5. Overview of submitted studies for tafamidis relevant to the single technology assessment.

ATTR-ACT (tafamidis)	
Study ID (NCT number)	ATTR-ACT (NCT01994889)
Study design	30-month, randomised, double-blind, placebo-controlled study
Study location(s)	Locations in United States, Belgium, Brazil, Canada, Czechia, France, Germany, Italy, Japan, Netherlands, Spain, Sweden and the United Kingdom (24)
Population	Patients with variant or wild-type ATTR-CM, n=441 Inclusion criteria: • Age ≥18 to ≤90 years • NYHA class I-III • Clinical HF with ≥1 previous hospitalisation for HF or clinical evidence for HF • NT-proBNP level ≥600 pg per mm • 6MWT >100 m • LV wall thickness ≥12 mm Exclusion criteria: • eGFR <25 mL/min/1.73 m^2 for the intention-to-treat population • Prior heart transplantation or implanted cardiac mechanical assist device • Prior liver transplantation • AL amyloidosis • Abnormal liver function tests • Prior treatment with tafamidis Stratification factors (patients were stratified at randomisation): • NYHA functional classification • Transthyretin genotype (wild type or variant)
Intervention	Tafamidis meglumine 80 mg daily (n=176) and tafamidis meglumine 20 mg daily (n=88) 80 mg of tafamidis meglumine is equivalent to 61 mg of tafamidis. Note that only tafamidis 61 mg is marketed in Norway for ATTR-CM.
Comparator	Placebo (n=177)
Primary endpoint	Hierarchical analysis over a 30-month period of (22): • ACM • Cumulative frequency of CV-related hospitalizations
Important secondary endpoint(s)	• 6MWT: change from baseline to month 30 • KCCQ-OS: change from baseline to month 30 • ACM • CV-related hospitalization • TTR stabilisation (27)
Observation time	Efficacy assessments are conducted at baseline, 6-month intervals and at month 30 (the end of the study) or at the time of patient discontinuation. If discontinuation occurred prior to month 30, a vital status follow-up was conducted at month 30 to assess their mortality status. Safety assessments were conducted at baseline and at clinic visits until month 30 (the end of the study) or patient discontinuation (23).

Data cuts	No formal efficacy interim analysis was planned. Assessments were conducted after study participants had been on treatment for 30 months (predefined analysis) (28). Data cut-off: 15/02/2018 (29)
Was the study part of the EMA MA approval process relevant for this STA?	☒ Yes ☐ No

Abbreviations: 6MWT = Six-minute Walk test; ACM = All-cause mortality; ATTR-CM = transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; HF = heart failure; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score; LV = left ventricular; MA = Market authorisation; NCT = national clinical trial; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; STA = single technology assessments; TTR = transthyretin
Source: (18-20, 22-25)

2.3.1 ITC methodology

The ITC was conducted via a matching-adjusted indirect comparison, MAIC, as base case for efficacy outcomes, and Bucher analysis as base case for safety outcomes. Both analyses use relative efficacy from individual trials as input parameters, with placebo as a common comparator (i.e. anchored analysis).

Bucher's method is a commonly used statistical approach for performing ITC. It provides a framework for estimating the relative treatment effect between two interventions (A and B) by leveraging their effects relative to a common comparator (C). The key assumptions behind the Bucher analysis are similarity of patient populations, study design, and outcome measures, homogeneity in the treatment effects across studies, and the presence of a valid common comparator (C).

Since Bayer identified important differences in patient characteristics across the studies, MAIC was chosen as a base case method for efficacy outcomes as the method allows for balancing patient characteristics between the trials. In this case, individual acoramidis-treated participants from the ATTRibute study (acoramidis and placebo) are assigned statistical weights that adjust for their over- or underrepresentation relative to the average treatment effect modifiers observed in ATTR-ACT (tafamidis and placebo). These weights are then incorporated into the analyses. An anchored MAIC analysis requires identification and inclusion of all effect modifying factors, but not prognostic factors.

Bayer has identified the following effect modifiers for efficacy outcomes, based on input from three independent key opinion leaders (KOL):

- NYHA class
- NT-proBNP (potential)
- eGFR (potential)
- TTR genotype (variant vs wild-type) (suggested as potential effect modifier by one KOL)

NT-proBNP and eGFR were ranked as potential effect modifiers, although the KOLs indicated that the effect of treatment may differ in patients with extreme values, such as NT-proBNP ≥8,500 pg/ml or eGFR < 20 mL/min/1.73m2 or age ≥75. All other characteristics were ranked as either prognostic factors, or neither effect modifier nor prognostic factor.

For safety outcomes, the three KOLs consulted by Bayer agreed that no baseline characteristic represented an effect modifier. Consequently, Bayer chose the Bucher approach for the safety outcomes.

Bayer has delivered results for both the ITT population and for the NYHA I + II subgroup that is eligible for acoramidis in the Norwegian clinical practice.

The NYHA class I/II subgroup from ATTRibute-CM was constructed by selecting patients with NYHA class I or II (344 in the acoramidis arm and 179 in the placebo arm) and excluding patients whose age exceeded the minimum and maximum ages of ATTR-ACT, those with baseline eGFR < 25 mL/min/1.73m², and those with screening NT-proBNP < 0.6 ng/mL.

Bayer has presented the following scenarios for the MAIC analysis in the NYHA I + II subgroup:

- Scenario 1 matched on eGFR*, NT-proBNP, NYHA Class, and TTR genotype
- Scenario 2 matched on eGFR*, NT-proBNP, and NYHA Class
- **Scenario 3 matched on eGFR*, NT-proBNP, NYHA Class, TTR genotype, and age (mean, median) (base-case)**
- Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age
- Scenario 5 matched on eGFR*, NT-proBNP, NYHA Class, and age

* eGFR was not included in weighting, but the exclusion criteria were matched across trials.

Since patients in both arms of ATTRibute-CM could receive tafamidis after completing 12 months follow-up, and since the proportion of patients who received tafamidis was higher in the placebo group, Bayer delivered two types of analyses addressing two estimands. Under a **hypothetical approach**, patients who received tafamidis were censored at the time of switch, i.e. the treatment effect is estimated under the assumption that the switch to tafamidis did not happen. Under an alternative estimand, the treatment effect is estimated regardless of the switch to tafamidis, i.e. data after the switch are used in the analysis.

NOMA's assessment
The evidence synthesis is considered valid for assessment of the relative efficacy of acoramidis vs. tafamidis. Bayer delivered a comprehensive and transparent technical report which included a clear description of the ITC methodology and presented results from the main analyses and various scenario analyses in the ITT population and the relevant NYHA class I/II subgroup. NOMA's evaluation will focus mainly on the results from the ITC in the NYHA I/II subgroup and use the ITC in the ITT population as support when needed.

2.4 Comparison of included studies

The premise for indirect comparisons is that the assumption of exchangeability is met. This requires that study design and patient characteristics are sufficiently comparable. MAIC adjusts for differences in patient populations between trials to reduce bias in the comparison. However, differences in endpoint definitions, follow-up durations, or measurement methods can introduce bias.

Table 6. Comparison of study designs.

	ATTRibute-CM (NCT03860935)	**ATTR-ACT (NCT01994889)**
Treatment Arms	Acoramidis HCl 800 mg (N=421) vs. Placebo (N=211)	Tafamidis 80 mg (N=176) vs. Tafamidis 20 mg (N=88) vs. placebo (N=177)
Data Cutoff	06 July 2023	15 February 2018
Study Design	RCT, Phase III, double-blind, multinational (18), multicenter (approx. 130)	RCT, Phase III, double-blind, multinational (13), multicenter (48)
Randomization Plan	2:1 ratio, stratification: TTR genotype (wild type vs. variant) NT-proBNP (≤ 3000 vs. >3000 pg/mL) eGFR (≥ 45 vs. < 45 mL/min/1.73 m^2)	2:1:2 ratio, stratification: TTR genotype (wild type vs. variant) NYHA class (I and II vs. III)
Study Initiation/ Completion	19 March 2019/11 May 2023	9 December 2013/7 February 2018
Treatment Period	Part A: 0–12 months Part B: 12–30 months with tafamidis allowed as a concomitant medication	0–30 months
Study Population	Patients with variant or wild-type ATTR-CM	Patients with variant or wild-type ATTR-CM
Key Primary 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	Hierarchical combination ACM and cumulative frequency of CV-related hospitalizations over the duration of the trial
Secondary/ Other 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 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	CFB in 6MWT/KCCQ-OS to month 30, ACM, CV-related mortality, frequency of CV-related hospitalization, TTR stabilization at month 1, and safety Exploratory: EQ-5D-3L

Table 7. Comparison of inclusion and exclusion criteria in the RCT's of acoramidis and tafamidis.

Study Name (ID)	**ATTRibute-CM (NCT04882735)**	**ATTR-ACT (NCT01994889)**
INCLUSION CRITERIA		
Diagnosis	ATTR-CM with wild-type TTR or a variant TTR genotype	ATTR-CM with either wild-type TTR or a variant TTR genotype
Age	18–90	18–90
Medical History	HF with at least one prior hospitalization for HF, clinical evidence of HF (without hospitalization) manifested by signs/symptoms of volume overload or elevated intracardiac pressures, or HF symptoms that required or require ongoing treatment with a diuretic	HF with at least one prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures that required treatment with a diuretic for improvement
NYHA Class	Class I-III	Class I-III
6MWT	6MWT≥150 m at screening	6MWT>100 m at screening
NT-proBNP Level	NT-proBNP≥300 to <8500 pg/mL at screening	NT-proBNP≥600 pg/mL at screening
LV Wall Thickness	Interventricular septum or LV posterior wall thickness≥12 mm	Interventricular septal wall thickness>12 mm
EXCLUSION CRITERIA		
eGFR	ITT population: All randomized patients who received at least one dose of the study medication and had at least one post-baseline efficacy evaluation excluding patients with an **eGFR<15 mL/min/1.73 m^2** at screening Primary analysis: mITT population excluding patients with an **eGFR<30 mL/min/1.73 m^2** at screening Safety analysis: All patients who received at least one dose of the study medication	ITT population: All randomized patients who received at least one dose of the study medication and had at least one post-baseline efficacy evaluation excluding patients with an **eGFR <25 mL/min/1.73 m^2 at** screening Primary analysis: mITT population had the same definition as the ITT population Safety analysis: All patients who received at least one dose of the study medication
Heart Transplantation	Heart transplantation likely within a year of screening	Prior heart transplantation or implanted cardiac mechanical assist device
Liver Transplantation	No restriction reported	Prior liver transplantation
Amyloidosis	AL amyloidosis	AL amyloidosis

Liver Function	Abnormal liver function tests	Abnormal liver function tests
Prior Therapies	Prior treatment with tafamidis, marketed drug products lacking a labelled indication for ATTR-CM (e.g., diflunisal or doxycycline), or natural products or derivatives used as unproven therapies for ATTR-CM within 14 days prior to dosing. Prior treatment with patisiran, inotersen, or other gene silencing agent within 90 days for patisiran, 180 days for inotersen, and five half-lives for any other gene silencing agent prior to dosing.	Prior treatment with tafamidis
Concomitant Therapies	Requires treatment with calcium channel blockers with conduction system effects. The use of dihydropyridine calcium channel blockers is allowed. The use of digitalis is only allowed if required for the management of atrial fibrillation with a rapid ventricular response.	Requires treatment with nonsteroidal anti-inflammatory drugs, tauroursodeoxycholate and doxycycline, diflunisal, calcium channel blockers, or digitalis.
Modified BMI*	**No restriction reported**	**<600 kg/m^{2}g/L at screening**

* The modified BMI was calculated by multiplying the BMI [weight (kg)/height (meters squared)] by the serum albumin concentration (g/L).

2.4.1 NOMA's assessment

ATTRibute-CM was used as a source of data for acoramidis whereas ATTR-ACT was used as a source of data for tafamidis.

Both studies were randomized, multinational, placebo-controlled Phase III trials that included patients with wild-type or variant transthyretin amyloid cardiomyopathy (ATTR-CM). In the ATTRibute-CM trial, 20% of the recruited patients were from the United States, while 80% were from other countries. Out of 611 patients, 355 were recruited from the European Union. In the ATTR-ACT trial, the majority of patients (63%) were recruited from the United States. These differences in recruitment locations may have influenced the standard of care.

There was a difference in the definition of the primary and secondary endpoints between the studies. However, results from the individual components of the most clinically relevant endpoints; All-cause mortality (ACM, including an event of heart transplant and cardiac mechanical assist device, and liver transplantation (in ATTR-ACT only)), cumulative frequency of CV-related hospitalizations (CVH), change from baseline in 6-minute walk test (6MWT), and change from baseline in Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) were reported in both studies. The ATTRibute-CM trial included events of clinical interest (EOCIs) as CV-related hospitalizations, while the ATTR-ACT trial did not. EOCIs were defined as medical visits (e.g., emergency department/ward, urgent care clinic, or day clinic) of <24 hours in ATTRibute-CM. For the purpose of the ITC, EOCIs were excluded from the analyses to align with ATTR-ACT.

There were some differences in statistical methodology, but these were largely adjusted for in the ITC. ACM was analyzed with a Cox proportional hazard model in both trials, with treatment and baseline 6MWT as covariates in ATTRibute-CM and treatment and stratification factors as covariates in ATTR-ACT. In ATTR-ACT frequency of CV-related hospitalizations was analyzed using a Poisson regression model, while the ATTRibute-CM trial used a negative binomial model. For the purpose of ITC, the Poisson model was used in both trials. In ATTR-ACT, the 6MWT and KCCQ endpoints were analyzed with the mixed model for repeated measures (MMRM) without explicit imputation. To align with ATTR-ACT, all analyses in ATTRibute-CM were also done without imputation.

Patients in both arms of ATTRibute-CM were permitted to initiate therapy with open-label, commercial tafamidis as a concomitant medication if they had completed at least 12 months of blinded study. Consequently 14.9% in the acoramidis arm and 22.8% in the placebo arm received tafamidis in the ITT population [redacted] respectively, in NYHA class I/II subgroup). The reasons for the switch were not reported. The switch to an effective alternative confounds the results of the primary analysis conducted at Month 30. To address the issue of confounding, Bayer presented two analyses, one with censoring of patients at the time of switch to tafamidis (a hypothetical approach), and one without applying censoring. The limitation of the hypothetical approach is that censoring should be non-informative for the results to be valid. That may not be the case if the actual reasons for switching were related to the efficacy and safety of the randomized treatment. A higher treatment switch proportion in the placebo group suggests informative censoring.

The inclusion and exclusion criteria were quite similar between the studies. The main difference in inclusion criteria was a lower limit of NT-proBNP in ATTRibute-CM (≥300 pg/mL) than in ATTR-ACT (≥600 pg/mL) and higher requirements for 6MWT at screening, ≥150 m and ≥100m respectively. This allows for the inclusion of a slightly healthier patient population in ATTRibute-CM compared to ATTR-ACT. The main difference in exclusion criteria was exclusion of patients with eGFR<15 mL/min/1.73 m2 (indication of renal failure) from ATTRibute-CM vs eGFR <25 mL/min/1.73 m2 in ATTR-ACT. However, exclusion criteria with respect to eGFR were aligned in the ITC.

ATTRibute-CM was conducted from 2019 to 2023 and ATTR-ACT from 2013 to 2018. The difference in the timing of the studies affected the populations enrolled in the studies. This has been previously discussed in chapter 1.4. Patients in ATTR-ACT are believed to have a more advanced disease than in ATTRibute-CM, as evidenced by the higher proportion of patients with NYHA class III in the ITT population of ATTR-ACT. The availability of tafamidis combined with non-invasive methods to diagnose ATTR-CM has led to earlier detection of ATTR-CM, which has resulted in healthier patients being enrolled in subsequent trials of therapies (30).

In the NYHA class I/II subgroup, which is the focus for this assessment, [redacted] baseline eGFR values and [redacted] NT-proBNP values in ATTR-ACT may suggest [redacted] although survival at 30 months for the NYHA class I/II subgroups [redacted] (0.67 (37/114 events) in ATTR-ACT vs. [redacted] in weighted ATTRibute-CM). Baseline KCCQ-OS score was [redacted] (from post hoc analysis identified by NOMA (31)).

NOMA's conclusion on similarity of study design
Overall, the studies are considered sufficiently similar in terms of design to perform an ITC.

2.5 Comparison of patient characteristics

Table 8 below shows which variables were used in MAIC and how the characteristics differed between ATTR-ACT (reference) and ATTRibute-CM (index trial) before and after MAIC weighting. The overall objective of MAIC is to remove potential confounding from imbalances in baseline effect modifiers.

Weight distribution diagrams are presented below (Figure 1 and Figure 2). The weight distribution was [redacted]

Table 8. Comparison of baseline characteristics for NYHA class I/II subpopulation, submitted by Bayer.

	ATTRibute-CM		ATTR-ACT	
	Acoramidis (N=344)	Placebo (N=179)	Tafamidis 80mg (N=121)	Placebo (N=114)
Age (years)				
Mean (SD)	[redacted]	[redacted]	75.0 (7.1)	73.1 (6.46)
Median (Q1, Q3)	[redacted]	[redacted]	75 (NR, NR)	74 (NR, NR)
Min, Max	[redacted]	[redacted]	56, 88	53, 86
Age >=65, n(%) Yes	[redacted]	[redacted]	NR	NR
Age >=80, n(%) Yes	[redacted]	[redacted]	NR	NR
Male sex, n(%)	[redacted]	[redacted]	113 (93.4%)	105 (91.1)
Race, n(%)				
Asian	[redacted]	[redacted]	8 (6.6%)	4 (3.5%)
Black	[redacted]	[redacted]	9 (7.3%)	16 (14.0%)
Not Reported	[redacted]	[redacted]	0	0
Other	[redacted]	[redacted]	2 (1.7%)	0
White	[redacted]	[redacted]	102 (84.3%)	94 (82.5%)
Ethnicity, n(%)				
Hispanic or Latino	[redacted]	[redacted]	NR	NR
Not Hispanic or Latino	[redacted]	[redacted]	NR	NR
Not Reported or Unknown	[redacted]	[redacted]	NR	NR
Genotype, n(%)				
ATTRm-CM	[redacted]	[redacted]	22 (18.2%)	24 (21.1%)
ATTRwt-CM	[redacted]	[redacted]	99 (81.8%)	90 (78.9%)
NYHA Class, n(%)				
NYHA CLASS I	[redacted]	[redacted]	13,20 %	11,40 %
NYHA CLASS II	[redacted]	[redacted]	86,80 %	88,60 %
Body Mass Index at Baseline (kg/m^2)				
Mean (SD)	[redacted]	[redacted]	25.90 (3.290)	25.88 (3.495)
Median (Q1, Q3)	[redacted]	[redacted]	NR	NR
Min, Max	[redacted]	[redacted]	NR	NR
Missing	[redacted]	[redacted]	NR	NR
NT-proBNP (ng/mL)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (Q1, Q3)	[redacted]	[redacted]	2.672 (1.7220, 4.2356)	2.816 (1.7660, 4.3600)
Min, Max	[redacted]	[redacted]	NR	NR
Six Minute Walk Test at Baseline (m)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (Q1, Q3)	[redacted]	[redacted]	383 (310, 451)	409 (327, 475)
Min, Max	[redacted]	[redacted]	NR	NR

Missing	[redacted]	[redacted]	NR	NR
KCCQ-OS				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (Q1, Q3)	[redacted]	[redacted]	NR	NR
Min, Max	[redacted]	[redacted]	NR	NR
Missing	[redacted]	[redacted]	NR	NR
eGFR at Baseline (mL/min/1.73 m2)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (Q1, Q3)	[redacted]	[redacted]	NR	NR
Min, Max	[redacted]	[redacted]	NR	NR
Duration of ATTR-CM (years)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median (Q1, Q3)	[redacted]	[redacted]	NR	NR
Min, Max	[redacted]	[redacted]	NR	NR
Missing	[redacted]	[redacted]	NR	NR
Geographic Region, n(%)				
Rest of World	[redacted]	[redacted]	NR	NR
United States	[redacted]	[redacted]	NR	NR
Permanent Pacemaker, n(%)	[redacted]	[redacted]	NR	NR
Implanted Cardiac Defibrillator, n(%)	[redacted]	[redacted]	NR	NR
Use of Diuretics, n(%)	[redacted]	[redacted]	NR	NR
Use of Antithrombotic Agents, n(%)	[redacted]	[redacted]	NR	NR
Use of Agents Acting on the Renin-angiotensin System, n(%)	[redacted]	[redacted]	NR	NR
Use of Beta-blockers, n(%)	[redacted]	[redacted]	NR	NR
Troponin I# (ng/mL)				
Median (Q1, Q3)	[redacted]	[redacted]	0.13 (0.08, 0.18)	0.13 (0.08, 0.18)
Smoking Classification, n(%)				
Never Smoker	[redacted]	[redacted]	65 (53.7%)	66 (57.9%)
Ex-Smoker	[redacted]	[redacted]	48 (39.7%)	42 (36.8%)
Smoker	[redacted]	[redacted]	6 (5%)	3 (2.6%)
Unspecified	[redacted]	[redacted]	2 (1.7%)	3 (2.6%)

In ATTR-ACT, Troponin I level missing for one placebo-treated patient. In ATTRibute-CM, the Troponin was not collected granularly below lower limit of quantification (LLWQ). [redacted]

References: Baseline characteristics for NYHA 1-2 subgroup of ATTR-ACT were obtained from:
Dutch Submission 2: Farmacotherapeutisch rapport tafamidis (Vyndaqel® 61 mg) bij de behandeling van ATTR-CM (https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2021/08/11/gvs-advies-tafamidis-vyndaqel-bij-de-behandeling-van-attr-cm/Brief+aan+minister+MZS+over+GVS+advies+herbeoordeling+tafamidis+%28Vyndaqel%29.pdf), p.91, Table 1.

Elliott, Perry, et al., Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. European Journal of Heart Failure 25.11 (2023): 2060-2064, Table 1. https://pubmed.ncbi.nlm.nih.gov/37434378/

Table 9. Comparison of baseline characteristics of the NYHA class I/II subgroup in ATTRibute-CM and ATTR-ACT, before and after MAIC adjustment.

Categories	**Reference tafamidis group**	**Unmatched acoramidis**	**Matched acoramidis**	**Reference placebo group from ATTR-ACT**	**Unmatched placebo from ATTRibute-CM**	**Matched placebo from ATTRibute-CM**
N or ESS	121	[redacted]	[redacted]	114	[redacted]	[redacted]
Proportion of NT-proBNP <2.672(Acoramidis) or <2.816(Placebo)ng/mL	0.5	[redacted]	[redacted]	0.5	[redacted]	[redacted]
Proportion of NT-proBNP <4.2356(Acoramidis) or <4.36(Placebo)ng/mL	0.75	[redacted]	[redacted]	0.75	[redacted]	[redacted]
Proportion of NT-proBNP<1.722(Acoramidis) or <1.766(Placebo)ng/mL	0.25	[redacted]	[redacted]	0.25	[redacted]	[redacted]
Proportion of ATTR-CM wildtype	0.818	[redacted]	[redacted]	0.789	[redacted]	[redacted]
Proportion of age>75(Acoramidis) or >74(Placebo) years	0.5	[redacted]	[redacted]	0.5	[redacted]	[redacted]
Centered Age (Mean)	0	[redacted]	[redacted]	0	[redacted]	[redacted]
Proportion of NYHA Class: I	0.132	[redacted]	[redacted]	0.114	[redacted]	[redacted]
Centered Age (SD) (not matched)	0	[redacted]	[redacted]	0	[redacted]	[redacted]
Proportion of Age >=65 (not matched)	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]
Proportion of Age >=80 (not matched)	NA	[redacted]	[redacted]	NA	[redacted]	[redacted]

Figure 1. Rescaled weight in acoramidis group, NYHA class I/II subpopulation, ATTRibute-CM.

Figure 2. Rescaled weight in placebo group, NYHA class I/II subpopulation, ATTRibute-CM.

2.5.1 Norwegian clinical practice

According to medical experts recruited by the regional health authorities, the populations in both studies are largely representative of patients in Norwegian clinical practice, with some exceptions.

Norwegian patients are approximately the same age as the study participants, according to the recruited medical experts. About 1/10 of Norwegian patients are women, which aligns with the studies.

According to the medical experts, background treatments among patients in Norwegian clinical practice are aligned somewhere between the two studies, as reported for the ITT population (Appendix 2).

There are far more cases of variant ATTR-CM in the studies than in Norwegian clinical practice, where TTR variants have barely been identified. Among individuals of Norwegian descent, fewer than five cases of variant ATTR-CM have been detected, whereas variant ATTR-CM is more frequent in other countries.

In Norwegian clinical practice, few patients are diagnosed in NYHA Class I, which is due to the relatively low symptom burden. When patients are diagnosed in NYHA Class I, it is often due to incidental findings in cases where patients are being examined for something else but where suspicion of ATTR-CM arises for various reasons and lead to further investigation. However, in Norwegian

clinical practice, ATTR-CM is often not detected until patients are hospitalized. At that point, the patients most often have heart failure in NYHA Class III.

In 2024, 473 patients in Norway received tafamidis. Of these, 447 patients (95 %) were aged ≥ 70, 404 patients (85 %) ≥ 75 years, and 268 (57%) were aged ≥ 80 years. The proportion of women was 14% (n=66) according to numbers from the Norwegian Drug Registry (32).

2.5.2 NOMA's assessment

Comparison of study populations prior to MAIC adjustment

The NYHA class I/II subgroup from ATTRibute-CM was constructed by selecting patients with NYHA class I or II (344 in the acoramidis arm and 179 in the placebo arm) and excluding patients whose age exceeded the minimum and maximum ages of ATTR-ACT, those with baseline eGFR < 25 mL/min/1.73m², and those with screening NT-proBNP < 0.6 ng/mL. This resulted in [redacted] patients in the acoramidis arm and [redacted] in the placebo arm. Patient characteristic data available for the NYHA class I/II subgroup in ATTR-ACT was limited (Table 8). Patients in the NYHA class I/II subgroup of ATTRibute-CM [redacted] in the NYHA class I/II subgroup of ATTR-ACT ([redacted] vs. 50% were over age 75), had a [redacted] of wild-type ATTR-CM ([redacted] vs. 79%-82%), and [redacted] NT-proBNP < 1,722 ([redacted] vs. 25%) (33).

No information on co-medication was available in ATTR-ACT for the NYHA class I/II subgroup but the more comprehensive reporting in the ITT population might provide some insights (see Appendix 2). The ITT population in ATTR-ACT was less frequently treated with agents targeting the renin-angiotensin system, beta blockers, diuretics, and antithrombotic agents compared to the ITT population in ATTRibute-CM. Additionally, a smaller proportion of patients (5-7%) in ATTR-ACT had permanent pacemaker implants compared to ATTRibute-CM (19%). According to medical experts recruited by the regional health authorities this difference is likely due to different standards of best supportive care across the study centers. Co-medication in Norwegian patients lie somewhere between the two studies, according to the recruited medical experts. The medical experts explain that earlier diagnosis followed by prevention of amyloidosis with e.g. tafamidis are the main factors that influence ACM and CVH. Further, medical experts explain that some of the standard treatments of heart failure are not very effective or well-documented, as described in the European society of cardiology Cardiomyopathies 2021 guidelines (12). The medical experts further explain that it is not likely that differences in co-medication (both between studies and compared to clinical practice) will have a significant impact on ACM, as it is the overall disease burden, the patients NYHA class at the time of diagnosis, and ATTR-CM-targeted treatment that most significantly influence ACM in ATTR-CM patients. As previously mentioned, SGLT2 inhibitors may potentially have a beneficial effect on ACM, but this remains uncertain as of today.

Selection of variables for weighting

Bayer identified NYHA class, NT-proBNP, eGFR, age and TTR genotype as potential effect modifiers for efficacy based on the results of subgroup analyses and clinical input. No safety effect modifier was identified. NOMA's interpretation of subgroup results in ATTRibute-CM and ATTR-ACT across the four outcomes evaluated in the ITC (ACM, CVH, 6MWT, KCCQ-OS) supports the notion that these factors may influence the treatment effect (see Appendix 3). However, the subgroup results do not demonstrate a strong or consistent signal of effect modification across all endpoints, which may be attributed to the small sample size. For instance, tafamidis may be more effective in wild-type ATTR-CM in terms of reducing CVH, but the effect on ACM seems similar between variant and wild-type

subgroups (2). In contrast, acoramidis appears to have a consistently better effect in the variant subgroup in terms of 6MWT, ACM and CVH (26).

eGFR was not used for weighting due to the unavailability of the reference value for the 80 mg tafamidis arm within the NYHA class I/II subgroup from ATTR-ACT. NOMA has identified a post hoc analysis of the ATTR-ACT study where eGFR values were reported for the pooled 80 and 20 mg tafamidis arm within the NYHA I/II subgroup (31). In the analysis, mean eGFR for the pooled tafamidis group was 57 (SD 14.2) mL/min/1.73m² and 55.1(14.4) mL/min/1.73m² for placebo. This is [redacted] (MAIC-unadjusted baseline values for acoramidis and placebo in NYHA class I/II subgroup) [redacted] (MAIC-adjusted values). Acoramidis does not appear to have different efficacy in a subgroup of patients with eGFR of ≥45 mL/min/1.73m² in terms of ACM or CVH, but acoramidis seems to perform worse in patients with affected kidney function (eGFR of <45 mL/min/1.73m²) in terms of a functional outcome of 6MWT and KCCQ-OS ((26), subgroup analyses). Similarly, region (US vs. rest of the world) may have an impact on acoramidis's effect on 6MWT but was not used in weighting. The inability to adjust for eGFR and region could have biased the 6MWT results.

According to medical experts recruited by the regional health authorities, a difference in eGFR of 5 ml/min/1.73 m² could influence ACM and CVH in large populations. However, the difference referred to here is likely due to the fact that patients in ATTR-ACT were in a more advanced state of illness than patients in ATTRibute-CM. Medical experts inform that it is difficult to assess further how reduced eGFR may affect 6MWT and quality of life, beyond the fact that lower eGFR reflects frailty, which in turn is associated with a poor prognosis.

Subgroup analysis of baseline medication gives an inconsistent picture of acoramidis effect (see Appendix 3). For instance, co-medication with diuretics seem to decrease the effect of acoramidis vs placebo, whereas co-medication with a renin-angiotensin system agent appears to increase the effect. Baseline medication has not been reported for the NYHA I/II subgroup of the ATTR-ACT study. [redacted] Inability to adjust for co-medication in the MAIC for the NYHA I/II subgroup has unclear consequences.

Subgroup analyses separately for NYHA class I and II have not been conducted in the studies so the value of adjusting for the NYHA class in the MAIC analysis is unknown.

Comparison of study populations after MAIC adjustment

After MAIC adjustment, [redacted] Since the reference population was the ATTR-ACT population, the treatment effect calculated in the ITC is based on the ATTR-ACT population characteristics. [redacted]

Due to the small number of patient characteristics used for adjustment, the sample size loss was about [redacted] for acoramidis arm and [redacted] for the placebo arm resulting in an effective sample size (ESS) of [redacted] and [redacted] respectively. The [redacted] ESS [redacted] in the placebo arm of ATTRibute-CM was likely due to [redacted] vs 13% for tafamidis, and [redacted] vs 11% for placebo in ATTR-ACT). The histograms of rescaled weight show [redacted]

The MAIC adjustment did not include potential effect modifying factors such as baseline medication, pacemaker, eGFR or country. In addition, as the reporting of patient characteristics was limited in the NYHA I/II subgroup of ATTR-ACT, it is unknown whether the MAIC adjustment introduced more imbalance in the remaining patient characteristics.

Overall, it is unclear whether MAIC adjustment reduced the overall bias of the ITC when compared to the unadjusted analysis (Bucher analysis). The results from both adjusted and unadjusted analyses will therefore be considered.

Generalizability

Based on data from the Norwegian Drug Registry on use of tafamidis in 2024, patients in the Norwegian clinical practice are somewhat older compared to the age in the ATTR-ACT study of tafamidis [redacted] The age of patients in the acoramidis study are closer to the age seen in Norwegian clinical practice. Subgroup analyses (Appendix 3) show that the protective effect of acoramidis is likely lower in patients ≥78 years old. In subgroup analysis of age within NYHA I + II, there was no effect on ACM of acoramidis in patients ≥78 years compared to placebo. In subgroup analysis, patients ≥78 years within NYHA I/II receiving acoramidis had a reduced risk of CVH compared to placebo, although the relative risk of CVH in patients <78 years was lower than in patients ≥78. The effect of acoramidis on 6MWT and KCCQ-OS was similar across subgroups of age within the NYHA I/II. Subgroup analysis of age within NYHA I/II was not available for tafamidis. For the ITT population, the subgroup analysis for tafamidis of age showed a lowered effect of tafamidis for ACM in older vs. younger patients, while the effect on CVH, 6MWT or KCCQ-OS was similar across age groups(Appendix 3). However, the use of 75 years as cut off in ATTR-ACT vs. 78 in ATTRibute-CM may impact these findings. With respect to differences in effect across age, the efficacy of acoramidis and tafamidis could be lower in the Norwegian clinical practice where patients are somewhat older.

Results showing a lower/absent efficacy of acoramidis in patients with NYHA III for several endpoints are not entirely unexpected. A similar pattern has been observed with tafamidis (26).

There are far more cases of variant ATTR-CM in the ATTR-ACT study of tafamidis [redacted] than in Norwegian clinical practice, where cases of variant ATTR-CM are hardly detected. Since the efficacy of acoramidis appears more profound in variant ATTR-CM in ATTRibute-CM, it is possible that overall efficacy of acoramidis is smaller in the Norwegian clinical practice. The treatment effect of tafamidis appears consistent across TTR genotypes. However, these subgroup analyses were all performed in the ITT population and may not be the same within the NYHA I/II subgroup.

The proportion of patients with pacemakers in Norwegian clinical practice is probably somewhere between the proportions in the two studies. Probably since ATTR-CM is not regularly screened for in patients with AV block, which is a common indication for pacemaker implantation. A higher proportion of patients in the acoramidis study are treated with beta-blockers and RAS inhibitors compared to Norwegian patients. As discussed above, it is unclear how co-medication will influence the effect of acoramidis.

Overall, there are some subtle differences between the MAIC scenarios and the Norwegian clinical practice that could potentially affect the effectiveness of acoramidis. However, how this translates into comparative efficacy vs tafamidis could not be determined.

NOMA's conclusion on similarity of patient characteristics

Reporting of patient characteristics in ATTR-ACT is very limited for the NYHA class I/II subgroup. Nevertheless, NOMA agrees that the most likely effect modifiers were identified and included in the

MAIC analysis. Prior to weighing there were some differences in age, genotype and NT-proBNP. Those differences were minimized upon weighting with small loss in sample size. The MAIC adjustment did not include potential effect modifying factors such as baseline medication, pacemaker, eGFR or region.

Overall, due to limited availability of patient characteristics, it is unclear whether MAIC adjustment reduced the overall bias when compared to the unadjusted analysis (Bucher analysis). The results from both adjusted and unadjusted analyses were therefore considered.

The effectiveness of acoramidis could potentially be different [redacted] However, how those differences affect comparative efficacy of acoramidis vs tafamidis remains unclear.

2.6 Relative efficacy

Relative efficacy and safety in the ITC are based on the subgroup analysis of NYHA class I/II and the ITT population from the acoramidis study presented in chapter 2.2 and the tafamidis study presented in chapter 2.3.

Results from data cut-off 06/07/2023 were used for ATTRibute-CM (1, 34, 35), whereas results from data cut-off 15/02/2018 were used for ATTR-ACT (27, 29).

Bayer has submitted results for subgroups of age (<78 and ≥78 years) within NYHA I/II from the ATTRibute-CM study of acoramidis. Due to lack of equivalent numbers in the ATTR-ACT study of tafamidis, an ITC for these subgroups was not possible to perform.

2.6.1 Submitted documentation

ITC results for the following efficacy endpoints in the NYHA class I/II populations are presented in this chapter:

- All-cause mortality (ACM) - (hazard ratio, HR [95% confidence interval, CI]) over 30 months
- CV-related hospitalizations - (relative risk ratio [95% CI]) over 30 months
- Change from baseline in distance walked during the 6MWT - (least square, LS, mean difference [95%CI]) over 30 and 12 months
- Change from baseline in the KCCQ-OS - (LS mean difference [95%CI])

Results from MAIC and Bucher analyses [redacted]

All-cause mortality (ACM)

Table 10. Hazard ratios from MAIC and Bucher analyses of ACM, NYHA class I/II subgroup.

Comparison	Hazard Ratio (95% CI), without cenzoring	Hazard Ratio (95% CI) with cenzoring
Acoramidis vs Placebo, Naive	[redacted]	[redacted]
Acoramidis vs Placebo, MAIC Scenario	[redacted]	[redacted]
Tafamidis 80mg vs Placebo, Naive RIPD (Censored at Month 30)	[redacted]	[redacted]
Acoramidis vs Tafamidis 80mg, Bucher analysis	[redacted]	[redacted]
Acoramidis vs Tafamidis 80mg, MAIC Scenario	[redacted]	[redacted]

HS- hypothetical strategy (with censoring for switch to tafamidis), RIPD- Reconstructed individual-patient data.Tafamidis 80mg and placebo RIPD were digitized from: Elliott, Perry, et al., Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. European Journal of Heart Failure 25.11 (2023): 2060-2064

Figure 3. KM plot for unadjusted and MAIC-adjusted ACM curves from ATTRibute-CM for NYHA I/II subgroup, with **no censoring due to switch tafamidis (upper panel)** and **with censoring, hypothetical approach (lower panel)**.

Cumulative incidence of CV-related hospitalization (CVH)

Table 11. Hazard ratios from MAIC and Bucher analyses of CVH, NYHA class I/II subgroup.

Comparison	Relative Risk Ratio (95% CI), without cenzoring	Relative Risk Ratio (95% CI), with cenzoring
Acoramidis vs. Placebo		
Tafamidis Pooled Dose vs. Placebo		
Acoramidis vs. Placebo (Weighted)		
Acoramidis vs. Tafamidis Pooled Dose, Bucher ITC		
Acoramidis vs. Tafamidis Pooled Dose (MAIC)		

The relative risk ratio (RRR) for tafamidis (pooled dos
Subgroup Analyses for Components of Primary Efficacy Composite. Clinical Review for 212161 and 211996, p.64, Center for Drug Evaluation and Research, Reference ID: 4411339.

Change from Baseline to Month 30 on quality of life measured with Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS)

Table 12. Least squares mean difference from MAIC and Bucher analyses of KCCQ-OS, NYHA class I/II subgroup.

Comparison	LS Mean Difference (95%CI), without cenzoring	LS Mean Difference (95%CI), with cenzoring
Acoramidis vs. Placebo	[redacted]	
Tafamidis Pooled Dose vs. Placebo		
Acoramidis vs. Placebo (Weighted)		
Acoramidis vs. Tafamidis Pooled Dose, Bucher ITC		
Acoramidis vs. Tafamidis Pooled Dose (MAIC)		

The least squares (LS) mean difference for tafamidis (pooled dose) vs placebo was obtained from Table 12 Study B3461028 KCCQ-OS Change from BL at month 30 (ITT, FDA Biometrics). Clinical Review for 212161 and 211996, p.64, Center for Drug Evaluation and Research, Reference ID: 4411339.

Change from Baseline to Month 30 on 6-minute walk test (6MWT)

Table 13. Least squares mean difference from MAIC and Bucher analyses of 6MWT, NYHA class I/II subgroup.

Comparison	LS Mean Difference (95%CI), without cenzoring	LS Mean Difference (95%CI), with cenzoring
Acoramidis vs. Placebo	[redacted]	
Tafamidis Pooled Dose vs. Placebo		
Acoramidis vs. Placebo (Weighted)		
Acoramidis vs. Tafamidis Pooled Dose, Bucher ITC		
Acoramidis vs. Tafamidis Pooled Dose (MAIC)		

The least squares (LS) mean difference for tafamidis (pooled dose) vs placebo was obtained from Table 11 Study B3461028 6MWT Change from BL, in meters, at month 30 (ITT, FDA). Clinical Review for 212161 and 211996, p.61, Center for Drug Evaluation and Research, Reference ID: 4411339.

2.6.2 NOMA's assessment

Results from the MAIC and Bucher analyses were presented for the approach with or without censoring (i.e. 4 analyses per endpoint).

All-cause mortality (ACM)

Results from the Cox regression model are only valid if the assumption of proportional hazards is met. However, the log cumulative hazard plot versus the log of time (not shown here) reveals clear crossing

of ACM curves between the treatment arms in ATTRibute-CM (both with and without weighting) and in ATTR-ACT, strongly suggesting that the assumption of proportional hazards is violated (not shown).

The results from the four analyses show [redacted] between acoramidis and tafamidis 80mg with respect to ACM. The point estimates vary, however, from [redacted] for the MAIC scenario without cenzoring to [redacted] for the Bucher scenario with cenzoring. These findings should be interpreted with caution due to the wide confidence intervals and the violation of the proportional hazard assumption. The MAIC adjustment [redacted] whereas censoring patients at the time of switching to tafamidis [redacted] Considering that tafamidis is an established treatment and that more patients switched in the placebo group, [redacted]

Cumulative incidence of CV-related hospitalization (CVH)

The findings from the four analyses [redacted] between acoramidis and the pooled dose of tafamidis in relation to CVH. The point estimates for the relative risk ratio, ranging from [redacted] Data for the NYHA class I/II subgroup was only available for the pooled dose of tafamidis. However, subgroup analyses based on tafamidis dosage demonstrated a very similar effect on CVH (36).

Change from Baseline to Month 30 on Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS)

The results from the four analyses [redacted] between acoramidis and the pooled dose of tafamidis in terms of KCCQ-OS. However, acoramidis demonstrated [redacted] The MAIC adjustment [redacted] for acoramidis. For the NYHA class I/II subgroup, only data for the pooled dose of tafamidis was available. Nonetheless, a subgroup analysis based on tafamidis dose indicated a very similar effect on KCCQ-OS ((36): table 12).

Change from Baseline to Month 30 on 6-minute walk test (6MWT)

Acoramidis [redacted] than tafamidis in the Bucher analysis of the 6MWT (least mean difference of [redacted] meters for the analyses without censoring). The MAIC analysis [redacted] meters for the analysis without censoring, corresponding to about [redacted] of baseline values as presented in Table 8). Censoring [redacted] According to the literature a change of approximately 30-32 meters can be considered to be clinically meaningful (37). Only pooled dose data for tafamidis was available for the NYHA class I/II subgroup. However, subgroup analyses based on tafamidis dose showed very similar effects on the 6MWT ((36): table 11).

There is [redacted] 6MWT is a performance-based outcome which may be influenced by individual and environmental factors that may challenge comparison across studies, despite using the same protocol.

NOMA's conclusion on relative effect
NOMA has not identified consistent differences in efficacy between acoramidis and tafamidis.

2.7 Adverse events

2.7.1 Submitted documentation

For the ATTRibute-CM study of acoramidis, 39/421 (9.3 %) in the acoramidis-arm and 13/211 (6.2 %) in the placebo arm discontinued treatment due to treatment emergent adverse events. Dose reduction was necessary in 4/421 patients (1.0 %) in the acoramidis-arm and 0 in the placebo-arm.

For the ATTR-ACT study of tafamidis, 40/176 (22.7 %) in the tafamidis 80 mg arm versus 51/177 (28.8 %) in the placebo arm discontinued treatment due to treatment emergent adverse events. The dose reduction was 2/176 (1.1 %) in the tafamidis-arm, and 4/177 (2.3 %) in the placebo-arm.

Table 14. Indirect treatment comparison of tafamidis versus acoramidis for safety outcomes, ITT population.

	ATTR-ACT: Observed Incidence and OR			**ATTRibute-CM: Observed Incidence and OR**			**ITC**
	Tafa 80 mg (N=176)	Placebo (N=177)	OR/RD (95% CI)	Acoramidis (N=421)	Placebo (N=211)	OR/RD (95% CI)	OR/RD (95% CI) (Acoramidis vs. Tafamidis) Bucher Analysis
TEAE	173 (98.3%)	175 (98.9%)	-0.57% (-3.04%, 1.89%)*	413 (98.1%)	206 (97.6%)	0.47% (-1.96%, 2.90%)*	1.044% (-2.419%, 4.507%)*
TESAE	133 (75.6%)	140 (79.1%)	0.82 (0.50, 1.35)	230 (54.6%)	137 (64.9%)	0.65 (0.46, 0.92)	0.796 (0.434, 1.457)
Severe TEAE	110 (62.5%)	114 (64.4%)	0.92 (0.60, 1.42)	157 (37.3%)	96 (45.5%)	0.71 (0.51, 1.00)	0.773 (0.447, 1.338)
TEAE related to study treatment	79 (44.9%)	90 (50.8%)	0.79 (0.52, 1.20)	50 (11.9%)	11 (5.2%)	2.45 (1.25, 4.81)	3.112 (1.407, 6.886)
TESAE related to study treatment	3 (1.7%)	4 (2.3%)	-0.56% (-3.46%, 2.35%)*	2 (0.5%)	0 (0.0%)	0.48% (-0.18%, 1.13%)*	1.030% (-1.950%, 4.011%)*
Patients discontinued drug due to TEAEs	40 (22.7%)	51 (28.8%)	0.73 (0.45, 1.17)	39 (9.3%)	18 (8.5%)	1.09 (0.61, 1.96)	1.506 (0.707, 3.209)
Patients with dose reduced due to TEAEs	2 (1.1%)	4 (2.3%)	-1.12% (-3.82%, 1.57%)*	4 (1.0%)	0 (0.0%)	0.95% (0.02%, 1.88%)*	2.074% (-0.773%, 4.921%)*
Common TEAs (all causalities)							
Cardiac failure	46 (26.1%)	60 (33.9%)	0.69 (0.44, 1.09)	101 (24.0%)	83 (39.3%)	0.49 (0.34, 0.69)	0.705 (0.395, 1.260)

Fall	43 (24.4%)	41 (23.2%)	1.07 (0.66, 1.75)	67 (15.9%)	39 (18.5%)	0.83 (0.54, 1.29)	0.778 (0.404, 1.499)
Dyspnea	29 (16.5%)	55 (31.1%)	0.44 (0.26, 0.73)	52 (12.4%)	40 (19.0%)	0.60 (0.38, 0.95)	1.377 (0.697, 2.718)
Peripheral edema	30 (17.0%)	31 (17.5%)	0.97 (0.56, 1.68)	33 (7.8%)	25 (11.8%)	0.63 (0.37, 1.09)	0.654 (0.300, 1.423)
Dizziness	25 (14.2%)	37 (20.9%)	0.63 (0.36, 1.09)	46 (10.9%)	23 (10.9%)	1.00 (0.59, 1.70)	1.600 (0.742, 3.453)
Congestive cardiac failure	22 (12.5%)	33 (18.6%)	0.62 (0.35, 1.12)	10 (2.4%)	7 (3.3%)	0.71 (0.27, 1.89)	1.137 (0.363, 3.562)
Atrial fibrillation	35 (19.9%)	33 (18.6%)	1.08 (0.64, 1.84)	70 (16.6%)	46 (21.8%)	0.72 (0.47, 1.08)	0.660 (0.337, 1.294)
Fatigue	29 (16.5%)	33 (18.6%)	0.86 (0.50, 1.49)	42 (10.0%)	26 (12.3%)	0.79 (0.47, 1.33)	0.916 (0.430, 1.951)
Constipation	26 (14.8%)	30 (16.9%)	0.85 (0.48, 1.51)	52 (12.4%)	32 (15.2%)	0.79 (0.49, 1.27)	0.928 (0.441, 1.953)
Cough	16 (9.1%)	30 (16.9%)	0.49 (0.26, 0.94)	32 (7.6%)	18 (8.5%)	0.88 (0.48, 1.61)	1.800 (0.744, 4.357)
Pain in extremity	27 (15.3%)	20 (11.3%)	1.42 (0.77, 2.64)	30 (7.1%)	11 (5.2%)	1.39 (0.68, 2.84)	0.981 (0.382, 2.520)

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

* Risk Difference (95% CI)

Note: Results shown in red significantly favor comparator

2.7.2 NOMA's assessment

EMA has assessed that the safety profile of acoramidis is acceptable in relation to the expected benefits through the procedure for granting marketing authorization. Differences between the intervention and the comparator in the occurrence of side effects, particularly those with significant impact on quality of life and/or resource use, are the most relevant aspects for the STA.

This STA has focused on the NYHA I/II subgroup, while data on adverse events were only available for the ITT population.

EMA mentions kidney injury in their summary of safety concerns for acoramidis, based on a slight increase in creatinine (approximately 15%) and decrease in eGFR (acoramidis: -8.2 mL/min and Placebo: -0.7 mL/min) (26). EMA concluded that neither analysis of the pivotal nor of the data across all 12 studies that were assessed during EMA's marketing approval process of acoramidis raise major concerns regarding safety.

According to the recruited medical experts, intolerance to tafamidis is very rare. Based on acoramidis' similar mode of action and the presented safety data, NOMA has not identified any consistent differences or causes for concern in adverse events between acoramidis versus tafamidis.

NOMA's conclusion on adverse events
NOMA has not identified consistent differences in adverse events.

3. Economic analysis

3.1 Cost-minimization analysis

The medicine acquisition costs in Bayer's submitted analysis is based on the maximal pharmacy retail price (AUP) excluding VAT for tafamidis (Vyndaqel 61 mg) and for acoramidis (Beyonttra 356mg) (Table 15).

Table 15. Medicine acquisition costs.

	Product number	**Strength**	**Pack size**	**Maximum AUP excluding VAT, pr. pack**	**Cost per 30 days of treatment*, max AUP excl. VAT.**
Acoramidis	532813	356 mg	120 tablets	NOK 100 532	NOK 100 532
Tafamidis	144490	61 mg	30 capsules	NOK 103 790	NOK 103 790

Abbreviations; AUP = Pharmacy retail price; VAT = value added tax; mg = milligram; NOK = Norwegian Krone
*According to summary of product, 4 tablets acoramidis á 356 mg daily (38), and 1 tablet á 61 tafamidis daily (17).

Tafamidis has a confidential, negotiated price that differs from the cost presented here.

Similar wastage is assumed for acoramidis and tafamidis.

NOMA assesses that other costs related to medicine acquisition, administration, health states and event costs, adverse events or miscellaneous costs are not relevant to present as these costs are assumed to be the same for the two medicinal products.

The corresponding yearly costs are thus NOK 1 223 139 for acoramidis, and NOK 1 262 778 for tafamidis, max AUP excl. VAT.

NOMA has not calculated budget impacts as this is a cost-minimization analysis. It is assumed that by an introduction of acoramidis in the market no new patients eligible for treatment will be generated additional to those already eligible for treatment with tafimidis. Given similar price by decision, no increased budget impact is assumed if acoramidis is introduced.

Bayer has the opportunity to participate in price negotiations. The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) will present a separate price summary with confidential prices.

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Appendix 1: Literature search

Submitted

The main study objective was to conduct a systematic literature review (SLR) of the available literature on wild-type or variant ATTR-CM patients covering clinical efficacy and safety.

Systematic literature searches were conducted on November 23, 2023, and updated on November 1, 2024, in Ovid (http://ovidsp.ovid.com/) to identify peer-reviewed studies of interest in the bibliographic databases listed in table 1, and complemented by various sources of grey literature. Hand searches for conference abstracts were conducted for those conferences not already indexed and captured in the Embase searches.

Table 1. Data sources in the clinical SLR

Clinical SLR		
Data source	Electronic databases	• Embase via Ovid • MEDLINE and MEDLINE In-Process via Ovid • Cochrane Central Register of Controlled trials • Cochrane Database of Systematic Reviews
	Grey literature	• Conference from the last 2 years: ACC, AHA, HFSA, ISA, ESC, ESCHF • Registries of ongoing clinical trials (ClinicalTrials.gov, WHO) • Hand-searching of the bibliographies of up to five relevant SLRs
Search limits	Publication date	• Full-texts: No limits • Conference abstracts: Last 2 years
	Geographical regions	None
	Language	English
	Timeframe	None

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; SLR = systematic literature review; WHO = World Health Organisation

The search strategy was conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database as recommended by the Cochrane Collaboration (39). The search strings were developed using guideline-recommended filters for specific search platforms to identify studies of relevant design for the different scope topics (40-42). Searches were restricted to studies conducted in humans and published in English.

The study selection process involved evaluating publications retrieved by the searches against predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria to establish which studies were eligible for inclusion in the SLR. The PICOS for the SLR topic on clinical efficacy and safety is described in table 2.

Table 2. PICOS inclusion and exclusion criteria – clinical SLR

Domain	Inclusion Criteria	Exclusion Criteria
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
Interventions	• Acoramidis (AG10) • Tafamidis • Inotersen • Patisiran • Vutrisiran • Diflunisal • Eplontersen • Organ transplant	Nonpharmacological interventions other than organ transplant (e.g., supplements)
Comparators	• Interventions, as above • Placebo • Best supportive care/symptomatic management • None (e.g., single-arm trials)	N/A
Outcomes	<u>Efficacy</u> • Overall survival • CV-related mortality • All-cause hospitalizations • CV-related hospitalizations (including urgent HF visits) • Functional exercise capacity (e.g., 6MWT) • Cardiac biomarkers (BNP level, troponin, eGFR) • Signs and symptoms of heart failure (e.g., breathlessness, NYHA class, NAC stage) • Serum TTR • TTR stabilization • Cardiac imaging in ATTR population (ECHO, PET scan, CMR) • Change in LV wall thickness • Change in LV GLS <u>Safety</u> • Total AEs • Total serious AE • Discontinuations due to AEs • Drug-related AEs <u>HRQoL</u> • General instruments (e.g., EQ-5D, SF-36) • Disease-specific instruments (e.g., KCCQ) • Patient and caregiver HRQoL	Outcomes not of interest
Study design	• 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

Abbreviations: 6MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; BNP = brain natriuretic peptide; CMR = cardiovascular magnetic resonance; CV = cardiovascular; ECHO = echocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5 Dimensions; GLS = global longitudinal strain; HF = heart failure; HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MA = meta-analysis; N/A = not applicable; NAC = National Amyloidosis Centre; NYHA = New York Heart Association; PET = positron emission tomography; PICOS = population, interventions and comparisons, outcomes, and study design; RCT = randomised controlled trial; SF-36 = 36-item Short Form Health Survey; SLR = systematic literature review; TTR = transthyretin

In the original SLR, 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 by two independent reviewers. Following title and abstract screening, 83 abstracts were deemed potentially relevant and assessed at the full-text level by two independent reviewers, resulting in 39 included publications reporting on 10 trials.

Updated searches for all databases were conducted on November 1, 2024, and yielded 222 records identified from bibliographic databases and 6 records from grey literature searches. After removing duplicates across databases and from previous searches, 104 were screened. Following title and abstract screening by two independent reviewers, 26 abstracts were deemed potentially relevant and assessed at the full-text level by two independent reviewers, resulting in 21 included publications. With the previous included records (N=38; search date: November 23, 2023), this resulted in a total of 59 publications reporting on 15 trials.

Data were extracted into data extraction tables (DETs), one for each topic review. The data were extracted into the DETs by one reviewer, and a second reviewer assessed the entries to ensure consistency and accuracy against the source article as a validation step. A third reviewer will be consulted to resolve disagreements, as necessary.

Risk of bias was assessed. The two studies relevant to this STA were both evaluated as Low risk of bias.

NOMA's assessment

The literature search is sufficiently updated 4 months ago and within the requirements of NOMA. The search strategy, selection of studies and results are sufficiently documented. The PICO is relevant for the STA. The systematic literature review seems to be executed and reported in line with the PRISMA guidelines for systematic reviews.

Selection of studies was performed by two independent reviewers in two steps, and discrepancies resolved with a third reviewer.

The submitted literature search is sufficiently documented and relevant for the STA.

Appendix 2: Baseline characteristics of the ITT populations in ATTRibute-CM and ATTR-ACT

Table 1. Comparison of baseline characteristics of the ITT populations in ATTRibute-CM and ATTR-ACT.

Trial		ATTRibute-CM (ITT)†		ATTR-ACT¥		
Treatment Arm	All Subjects (N=632)	Acoramidis (N=421)	Placebo (N=211)	Tafamidis (80 mg) (N=176)	Pooled Tafamidis (80 + 20 mg) (N=264)	Placebo (N=177)
Genotype, n (%)						
ATTRv	61 (9.7)	41 (9.7)	20 (9.5)	42 (23.9)	63 (23.9)	43 (24.3)
ATTRwt	571 (90.3)	380 (90.3)	191 (90.5)	134 (76.1)	201 (76.1)	134 (75.7)
NYHA class, n (%)						
I	68 (10.8)	51 (12.1)	17 (8.1)	16 (9.1)	24 (9.1)	13 (7.3)
II	455 (72.0)	293 (69.6)	162 (76.8)	105 (59.7)	162 (61.4)	101 (57.1)
III	109 (17.2)	77 (18.3)	32 (15.2)	55 (31.3)	78 (29.5)	63 (35.6)
Race, n (%)						
White	555 (87.8)	368 (87.4)	187 (88.6)	136 (77.3)	211 (79.9)	146 (82.5)
Black	30 (4.7)	20 (4.8)	10 (4.7)	26 (14.8)	37 (14.0)	26 (14.7)
Asian	13 (2.1)	10 (2.4)	3 (1.4)	11 (6.3)	13 (4.9)	5 (2.8)
Other	10 (1.6)	7 (1.6)	3 (1.4)	3 (1.7)	3 (1.1)	0
Not Reported	24 (3.8)	16 (3.8)	8 (3.8)	0	0	0
NT-proBNP (pg/mL)						
Mean (SD)‡	2872.4 (2145.1)	2946.1 (2226.0)	2725.4 (1970.8)	3,941.1 (3,090.0)	3,948.7 (3,382.3) *	3,845.5 (2,971.5)
Median (Min, Max) ‡	2325.5(277,15711)	2326.0 (280, 15711)	2306.0 (277, 8829)	3122 (392.0, 22020.1)	2995.9	3161 (298.0, 16787.1)
IRQ ‡	1281.8, 3897.8	1132.0, 4019	1128.5, 3752	1826.0, 4948.5	1751.5, 4861.5	1864.4, 4825.0
Permanent pacemaker insert, n (%)						

Yes	120 (19.0)	81 (19.2)	39 (18.5)	NR	13 (4.9)	12 (6.8)
Age (years)						
Mean (SD)	77.27 (6.552)	77.37 (6.450)	77.09 (6.763)	75.2 (7.2)	74.5 (7.2)	74.1 (6.7)
Median (Min, Max)	78.0 (50, 90)	78.0 (50.3, 90.8)	78.0 (55, 91)	76.0 (46, 88)	75 (46, 88)	74.0 (51, 89)
≥65, n (%)	611 (96.7)	409 (97.1)	202 (95.7)	160 (90.9)	237 (89.8)	162 (91.5)
≥80, n (%)	244 (38.6)	161 (38.2)	83 (39.3)	51 (29.0)	NR	37 (20.9)
Sex, n (%)						
Male	570 (90.2)	384 (91.2)	186 (88.2)	158 (89.8)	241 (91.3)	157 (88.7)
Female	62 (9.8)	37 (8.8)	25 (11.8)	18 (10.2)	23 (8.7)	20 (11.3)
Implanted cardiac defibrillator, n (%)						
Yes	43 (6.8)	26 (6.2)	17 (8.1)	NR	16 (6.1)	9 (5.1)
Ethnicity, n (%)						
Hispanic/ Latino	12 (1.9)	8 (1.9)	4 (1.9)	4 (2.3)	7 (2.7)	7 (4.0)
Not Hispanic/ Latino	600 (94.9)	401 (95.2)	199 (94.3)	171 (97.2)	255 (96.6)	170 (96.0)
Not Reported or Unknown	20 (3.1)	12 (2.9)	8 (3.8)	1 (0.6)	2 (0.8)	0
BMI (kg/m2)						
Mean (SD)	27.05 (3.781)	27.07 (3.793)	27.01 (3.766)	26.32 (3.805)	26.22 (3.752)	26.33 (4.277)
Min, Max	18.1, 42.7	18.1, 42.7	19.3, 40	18, 40	16, 40	16, 48
Duration of ATTR-CM (years)						
Mean (SD)	1.20 (1.201)	1.24 (1.203)	1.12 (1.195)	0.932 (1.1789)	1.023 (1.3259)	1.233 (1.4388)
Median (Min, Max)	0.79 (0, 10.1)	0.84 (0, 10.1)	0.71 (0, 7.4)	0.561 (0.003, 6.888)	0.559 (0.003, 9.958)	0.671 (0.003, 7.888)
6MWT (m)						
Mean (SD)	356.91 (100.531)	361.21 (103.705)	348.37 (93.564)	NR	350.55 (121.296)	353.26 (125.983)
Median (Min, Max)	354.37 (150.6, 695.8)	362.68(150.6, 695.8)	348.87 (151.1, 598.4)	342.5 (61, 685)	354 (24, 685)	346 (80, 822)
KCCQ-OS, mean (SD)						
Overall summary score***	TBD	71.5 (19.4)	70.3 (20.5)	NA	67.28 (21.36)	65.90 (21.74)
Baseline Medications, n (%)						

Agents acting on renin-angiotensin system	276 (43.7)	188 (44.7)	88 (41.7)	NA	69 (26.1)	48 (27.1)
Beta blockers	291 (46.0)	194 (46.1)	97 (46.0)	NA	76 (28.8)	53 (29.9)
Diuretics	540 (85.4)	359 (85.3)	181 (85.8)	NA	175 (66.3)	123 (69.5)
Antithrombotic agents	511 (80.9)	342 (81.2)	169 (80.1)	NA	105 (39.8)	72 (40.7)
Country						
Asia	24 (3.8)	19 (4.5)	5 (2.4)	10 (5.7)	12 (4.5)	5 (2.8)
Canada	32 (5.1)	19 (4.5)	13 (6.2)	1 (0.6)	1 (0.4)	0
Europe	344 (54.4)	227 (53.9)	117 (55.5)	56 (31.8)	79 (29.9)	63 (35.6)
South America	7 (1.1)	5 (1.2)	2 (0.9)	1 (0.6)	1 (0.4)	1 (0.6)
United States	126 (19.9)	80 (19.0)	46 (21.8)	108 (61.4)	171 (64.8)	108 (61.0)
Australia and New Zealand	99 (15.7)	71 (16.9)	28 (13.3)	0	0	0
Region						
US	126 (19.9)	80 (19.0)	46 (21.8)	108 (61.4)	171 (64.8)	108 (61.0)
Non-US	506 (80.1)	341 (81.0)	165 (78.2)	68 (38.6)	93 (35.2)	69 (39.0)

Appendix 3: Data-Driven Evidence for Effect Modification

SUBGROUP ANALYSES IN ATTRIBUTE-CM

Figure 14.2.1.53
Forest Plot for Hazard Ratio of All-Cause Mortality by Overall and Subgroup Analysis
mITT Population

Subgroup	No.(%) of Patients	Hazard Ratio [95% CI]	p-value
Overall	611(100.0)	0.772 [0.542, 1.102]	0.1543
ATTR-CM Genotype			0.1785*
ATTRm-CM	59(9.7)	0.450 [0.195, 1.040]	0.0619
ATTRwt-CM	552(90.3)	0.850 [0.575, 1.256]	0.4142
NT-proBNP (pg/mL)			0.5420*
<= 3000	401(65.6)	0.857 [0.493, 1.490]	0.5855
> 3000	210(34.4)	0.686 [0.433, 1.085]	0.1070
eGFR (mL/min/1.73m2)			0.7590*
< 45	94(15.4)	0.858 [0.387, 1.903]	0.7057
>= 45	517(84.6)	0.746 [0.503, 1.107]	0.1460
Age (years)			0.1216*
< 78	299(48.9)	0.554 [0.321, 0.956]	0.0339
>= 78	312(51.1)	0.984 [0.611, 1.586]	0.9472
Country			0.7293*
United States	119(19.5)	0.873 [0.423, 1.805]	0.7149
Rest of World	492(80.5)	0.754 [0.501, 1.134]	0.1754
NYHA Class			0.2746*
I, II	512(83.8)	0.695 [0.466, 1.036]	0.0743
III	99(16.2)	1.145 [0.515, 2.546]	0.7400

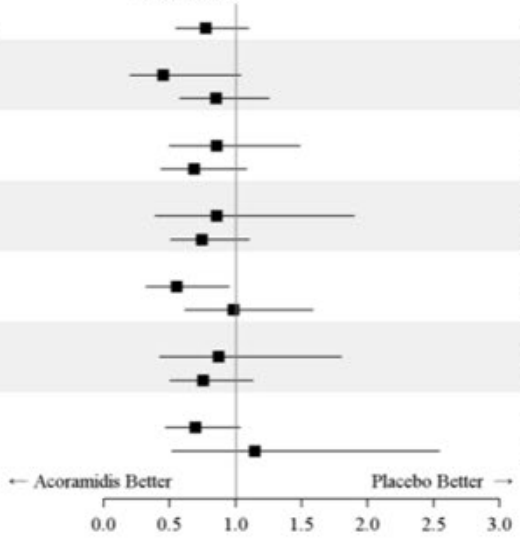


Figure 14.2.1.57
Forest Plot for Relative Risk Ratio of Cumulative Frequency of Cardiovascular-Related Hospitalization by Overall and Subgroup
mITT Population

Subgroup	No.(%) of Patients	Relative Risk [95% CI]	p-value
Overall	611(100.0)	0.496 [0.355, 0.695]	<0.0001
ATTR-CM Genotype			0.5685*
ATTRm-CM	59(9.7)	0.377 [0.139, 1.027]	0.0565
ATTRwt-CM	552(90.3)	0.514 [0.360, 0.734]	0.0002
NT-proBNP (pg/mL)			0.5124*
<= 3000	401(65.6)	0.456 [0.299, 0.695]	0.0003
> 3000	210(34.4)	0.576 [0.330, 1.003]	0.0514
eGFR (mL/min/1.73m2)			0.6587*
< 45	94(15.4)	0.594 [0.250, 1.415]	0.2397
>= 45	517(84.6)	0.481 [0.334, 0.692]	0.0001
Age (years)			0.4249*
< 78	299(48.9)	0.437 [0.275, 0.696]	0.0005
>= 78	312(51.1)	0.576 [0.353, 0.940]	0.0272
Country			0.9578*
United States	119(19.5)	0.488 [0.230, 1.037]	0.0622
Rest of World	492(80.5)	0.500 [0.343, 0.728]	0.0003
NYHA Class			0.3044*
I, II	512(83.8)	0.447 [0.310, 0.645]	<0.0001
III	99(16.2)	0.721 [0.313, 1.660]	0.4419

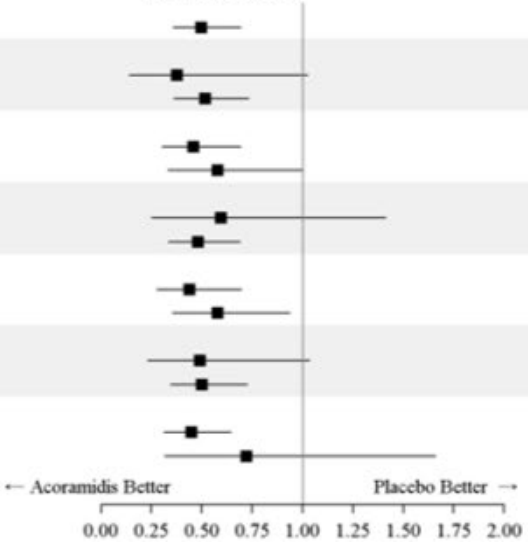


Figure 27: Forest Plot for Change From Baseline in 6MWD (meters) to Month 30 by Overall and Subgroup, mITT Population

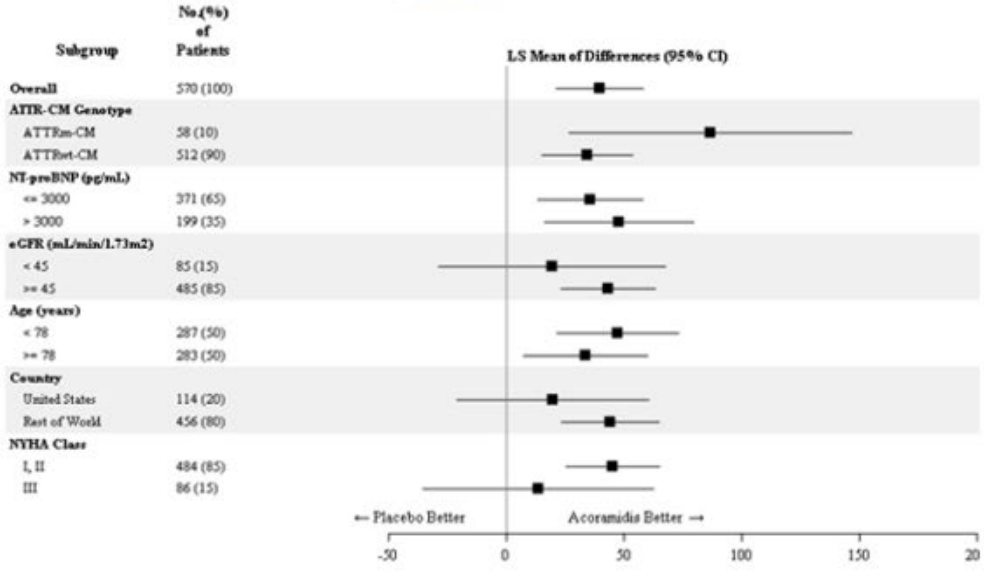
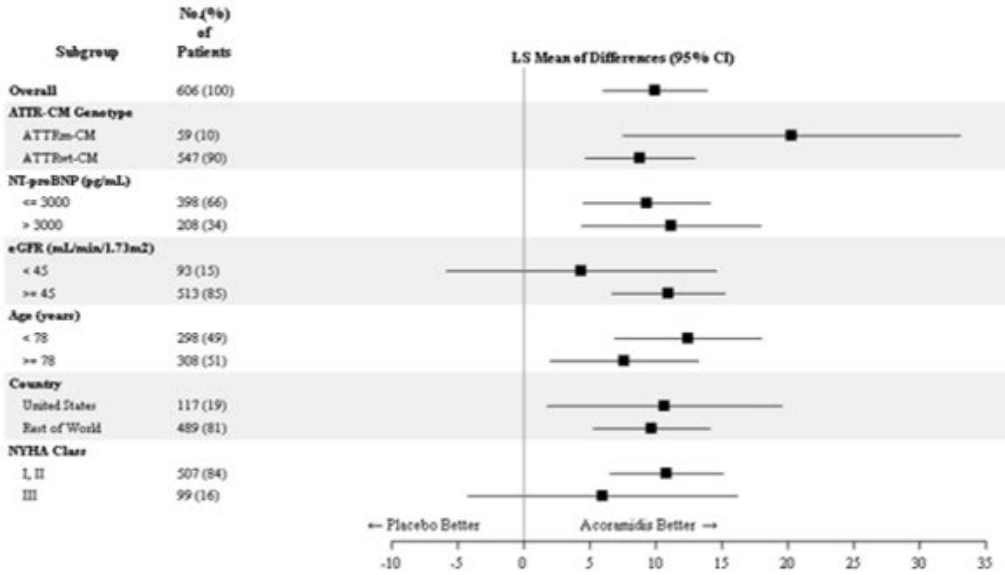
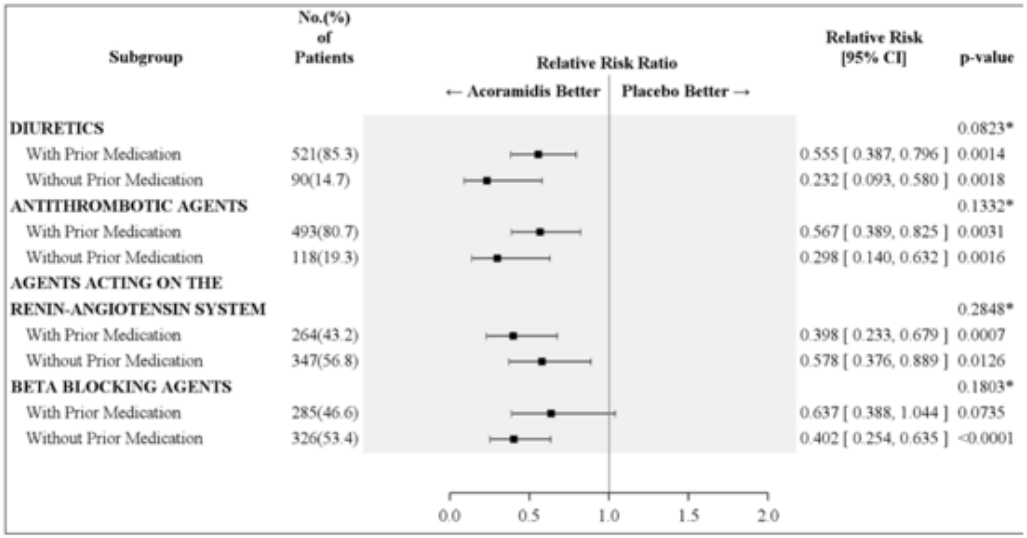


Figure 28: Forest Plot for Change From Baseline in KCCQ-OS to Month 30 by Overall and Subgroup, mITT Population

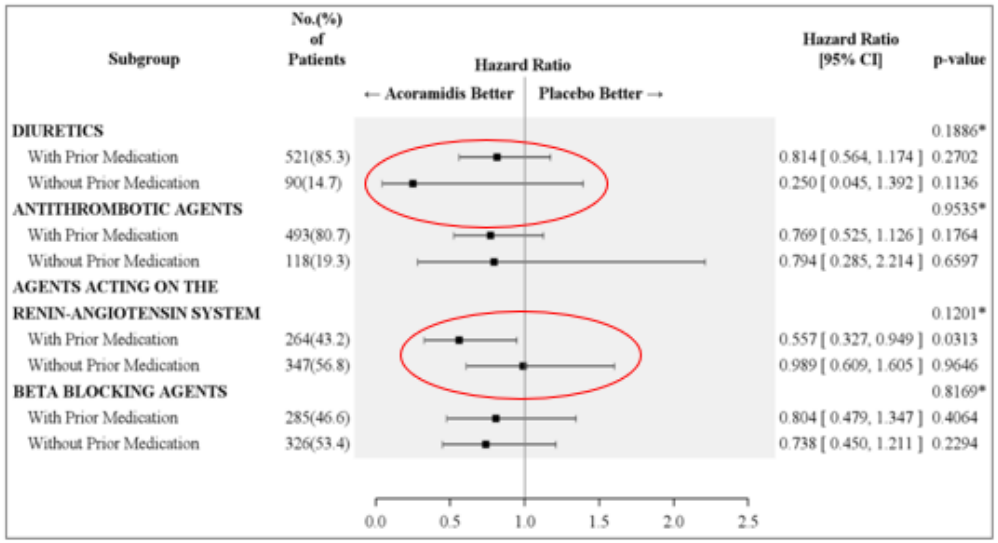


Source: ATTRibute-CM Clinical Study Report

Forest Plot for Relative Risk Ratio of Cumulative Frequency of Cardiovascular-Related Hospitalization by Baseline Medication Use, mITT Population



Forest Plot for Hazard Ratio of All-Cause Mortality by Baseline Medication Use, mITT Population



Source: ATTRibute Patient-level data on file

SUBGROUP ANALYSES IN ATTR-ACT

Figure 10 Study B3461028: Subgroup Analysis for Components of Primary Efficacy Composite

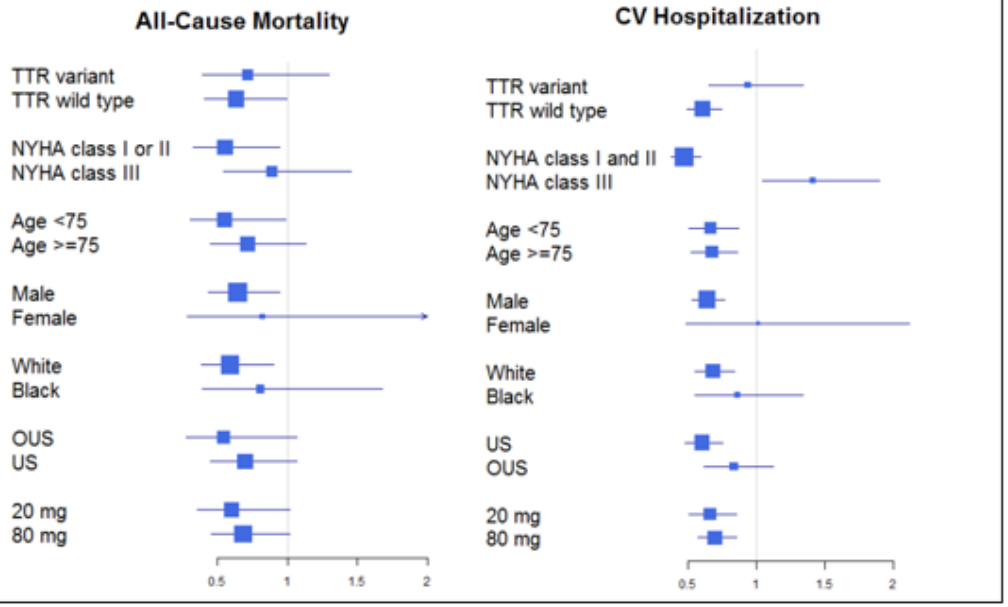
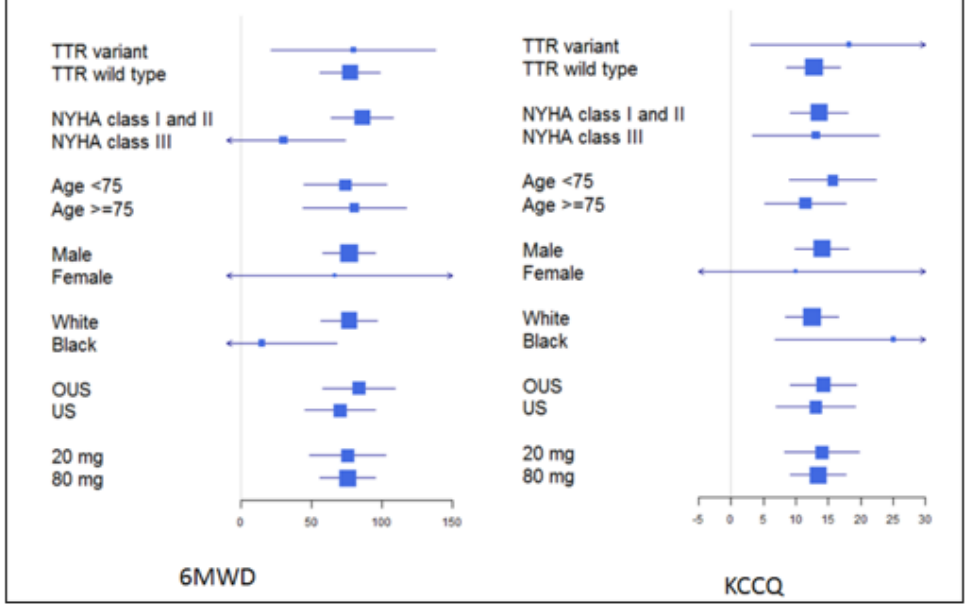


Figure 15 Study B3461028: Subgroup Analysis for 6MWT and KCCQ



Source: CDER Clinical Review APP#: 211996Orig1s000 (36).

Appendix 4: Innspill fra medisinske fageksperter rekruttert til oppdraget

Det er oppnevnt fire medisinske fageksperter til oppdraget om metodevurdering. Disse har bistått DMP med avklaringer rundt dagens behandling for pasientgruppen, forventet plassering av virkestoff i behandlingsalgoritmen, overførbarhet av studiedata til norsk pasientpopulasjon, og hvordan forskjeller mellom studiepopulasjonene kan påvirke de studerte endepunktene. DMP har benyttet disse innspillene i sine vurderinger gjennom rapporten.

De rekrutterte medisinske fagekspertene har i tillegg fått mulighet til å levere et 1-2 siders innspill til metodevurderingen. Dersom slike innspill foreligger, angis de nedenfor.

Det foreligger ingen ytterligere innspill fra rekrutterte medisinske fageksperter utover det som fremgår av rapporten.

Appendix 5: Kommentarer fra produsent

Bayer har fått mulighet til å levere en 1-2 siders kommentar som vedlegges rapporten og følger saken. Bayer har imidlertid valgt å avstå fra å gi en slik kommentar i denne saken.