12 December 2024
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EMADOC-1700519818-1831757
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Beyonttra (acoramidis)
Treatment of ATTR amyloidosis
EU/3/18/2081

Sponsor: BridgeBio Europe B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid
Other name(s)	-
International Non-Proprietary Name	Acoramidis
Tradename	Beyonttra
Orphan condition	Treatment of ATTR amyloidosis
Sponsor's details:	BridgeBio Europe B.V. Weerdestein 97 1083 GG Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharma Gateway AB
COMP opinion	11 October 2018
EC decision	19 November 2018
EC registration number	EU/3/18/2081
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pharma Gateway AB to Bridge Bio Europe B.V. – EC decision of 26 November 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Fátima Ventura / Janet Koenig
Applicant	BridgeBio Europe B.V.
Application submission	7 January 2024
Procedure start	1 February 2024
Procedure number	EMA/H/C/0006333
Invented name	Beyonttra
Proposed therapeutic indication	BEYONTTRA is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Beyonttra
CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Joao Rocha / Elisabeth Johanne Rook
Sponsor's report submission	15 August 2024
COMP discussion and adoption of list of questions	5-7 November 2024
Oral explanation	3 December 2024
Sponsor's removal request	5 December 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid was considered justified based on preliminary clinical observations in ATTR-cardiomyopathy patients, showing improvements in serum prealbumin;
- the condition is life-threatening and chronically debilitating in particular due to the development of polyneuropathy and cardiomyopathy;
- the condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in ATTR-amyloidosis patients with cardiomyopathy, who responded to treatment with stabilization of transthyretin and increase of serum concentration of transthyretin. The authorised products are indicated for polyneuropathy manifestations. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid as an orphan medicinal product for the orphan indication: treatment of ATTR amyloidosis. "

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Transthyretin-mediated (ATTR) amyloidosis is a rare, progressive disease caused by the misfolding of the transthyretin (TTR) protein. This protein is primarily produced in the liver and normally helps transport vitamin A and thyroxine (a thyroid hormone) in the blood.

In ATTR amyloidosis, the misfolded TTR proteins aggregate into amyloid fibrils, which deposit in various tissues and organs, leading to their dysfunction. There are two main types of ATTR amyloidosis:

Hereditary with variant (vTTR): This hereditary form is caused by mutations in the TTR gene and can affect multiple organs. Variant type hATTR is almost in all cases associated with polyneuropathy, but it can also be associated with cardiac ATTR (ATTR-CM), ATTRwith polyneuropathy or mixed forms, depending on the observed disease phenotype. Several vTTR gene variants have been associated with hATTR, with the Val30Met variant being the most common worldwide. The Val30Met variant primarily causes neuropathic symptoms when associated with early disease onset (before 50 years of age), while both neurologic and cardiac involvement is observed in late-onset V30M. hATTR is generally inherited in an autosomal dominant pattern.

Wild-type (wtATTR): This form occurs without any known specific genetic mutations and primarily affects the heart. The average age at diagnosis for wtATTR is around 75 years and the great majority of cases reported are males. The condition has previously been known as Senile Systemic Amyloidosis.

The approved therapeutic indication "BEYONTTRA is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)" falls within the scope of the designated orphan condition "treatment of ATTR amyloidosis".

Intention to diagnose, prevent or treat

The medical plausibility will be confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

hATTR is a life-threatening and debilitating condition. ATTRv is a progressively debilitating disease that leads to premature death. Patients with ATTRv typically present with polyneuropathy, carpal tunnel syndrome, autonomic insufficiency, cardiomyopathy, and gastrointestinal features, occasionally accompanied by vitreous opacities and/or renal insufficiency. The clinical course of ATTRv usually progresses over 5 to 15 years and ends with death from cardiac failure, renal failure, or malnutrition (OMIM 105210). Wild type ATTR- CM is also potentially life-threatening, more common among elderly and men with a main clinical presentation of biventricular congestive heart failure. Cardiac symptoms are usually present when the amyloid deposits are extensive enough to produce an increase in left ventricular wall thickness. Prognosis is poor in patients with untreated ATTR-CM, with median survival estimates of 2 to 6 years after diagnosis, depending on factors such as genotype and stage of disease (Shah et al, 2023). It is noted that wtTTR in cardiac tissue is a common finding in autopsies in (very) elderly, but these are not always associated with signs or previous symptoms of CM (Tanskanen, M., et al., 2008. Annals of Medicine, 40(3), 232–239. https://doi.org/10.1080/07853890701842988).

Although new treatment options have been authorised since the original orphan designation in 2018, the condition is still considered as chronically debilitating and life threatening.

Number of people affected or at risk

At the time of the initial ODD application, to estimate the point prevalence of ATTR amyloidosis, the sponsor applied the formula P=I×D, where P represents point prevalence, I indicates annual incidence, and D denotes mean disease duration. Based on data available at the time of the initial orphan designation application in 2018, the sponsor calculated a point prevalence of approximately 0.096 (rounded to 0.1) per 10,000 in the EU. This estimate utilized an annual incidence rate of 290 cases and a maximum survival duration of 16.9 years, as reported in earlier studies (Connors, 2016; Pinney, 2013; Sikora, 2015).

At the time of maintenance of the orphan designation in 2024, the sponsor updated this estimate by incorporating more recent data spanning from May 2018 to July 2024. The recalculated prevalence considered both main forms of ATTR amyloidosis: hereditary variant (ATTRv) and wild-type (ATTRwt). This combined approach is grounded in the latest prevalence data reported in recent literature (Table 1), reflecting a broader and more current understanding of the disease's epidemiology.

Due to a lack of comprehensive European-wide prevalence data, the sponsor leveraged data from Sweden, a country known for its relatively high prevalence rates of ATTRv amyloidosis. Specifically, the prevalence was estimated to be 2.5 per 10,000 for ATTRv in the Norrbotten region and 1.7 per 10,000 for ATTRwt in the Umeå region, culminating in a combined prevalence of 4.2 per 10,000. This calculation differentiates between the distinct aetiologies (ATTRv and ATTRwt) and aligns with orphan designation guidelines, which allow for extrapolation from regional data in the absence of EU-wide information.

With the updated Eurostat population estimate of 454,335,699 for the European Economic Area (EEA) in 2023, the sponsor's prevalence rate of 4.2 per 10,000 translates to an estimated 190,821 individuals living with ATTR amyloidosis within the region. The sponsor argues that this estimate is conservative, as it is based primarily on data from Sweden, which would be known to exhibit a higher prevalence of the disease compared to other European countries. The increase from the initial prevalence estimate would be attributed to advancements in diagnostic capabilities, which have improved disease detection and reporting. However, the publications used by the sponsor to calculate prevalence specifically of wtATTR go until 2018, that, although scintigraphy was already available, this novel diagnosis method was not yet fully introduced into clinical practice (nor into ATTR-CM diagnosis guidelines) and therefore would not accurately reflect the increase in diagnosis evidenced in the latest years.

Overall, while the sponsor has made initial efforts to estimate the prevalence for the proposed orphan condition, it is essential to ensure that the approach adheres to the established guidelines, such as those outlined in the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation", and that it is based on the current understanding of the disease. To enhance the reliability of the estimate, the sponsor should not only justify the selection of data sources and methodologies but also incorporate recent studies that capture the impact of advancements in diagnostic technologies, such as scintigraphy. These advancements have likely contributed to an apparent increase in the number of diagnosed cases, as reflected in recent publications such as Aimo, Alberto, et al. 2022; Aimo, Alberto, et al. 2024. Also, the aging population in the EU may be an important factor for increasing prevalence of ATTRwt. Although still to be determined, approved medicines specifically for cardiac amyloidosis might also be related to prolonged survival, potentially affecting prevalence calculations.

Additionally, the current prevalence calculation is based on several assumptions that could introduce variability, especially when extrapolated across different demographic segments within the European

Economic Area. To enhance the robustness of the prevalence estimate, the sponsor should conduct a thorough sensitivity analysis. This analysis should account for factors that might skew the estimate, such as overrepresentation of certain demographics (e.g., elderly patients, who may disproportionately increase prevalence figures) or underrepresentation of others, potentially leading to underestimation. A detailed exploration of how these underlying assumptions affect the overall estimate is essential, with an emphasis on using data sources that reflect current diagnostic practices. By addressing these areas and incorporating more precise, up-to-date epidemiological data, the sponsor should produce a more accurate and reliable estimate of the true prevalence of ATTR amyloidosis in the target population.

Ultimately, acknowledging the increase in diagnosed cases due to improved detection methods is important. This not only justifies the higher prevalence figure but also highlights the shifting landscape in the management and diagnosis of ATTR amyloidosis, which needs to be factored into future prevalence assessments to ensure future orphan designations remains valid and reflective of the current disease burden.

Table 1. Reported Prevalence of ATTR Amyloidosis.

Reference	Period	Subset	Country	Prevalence
(Mejia Baranda 2022)	2018	ATTRv	Norrbotten region, Sweden	2.5 per 10,000
(Lindmark 2021)	Between January 2010 and May 2018	ATTRwt	Umeå region, Sweden	1.7 per 10,000
(Russo 2020)	Based on the population census on 01 January 2019	ATTRv	Italy	447 subjects enrolled. Prevalence=0.0433 per 10,000
(Inês 2018)	2016	ATTRh-PN	Portugal	2.3 per 10,000
(Lauppe 2022)	2018	ATTR-CM	Denmark, Finland, Norway, Sweden	Denmark: 0.14 per 10,000 Finland: 0.18 per 10,000 Norway: 0.37 per 10,000 Sweden: 0.5 per 10,000

Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRh-PN = hereditary transthyretin amyloidosis polyneuropathy; ATTRv = variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The current pharmacological treatments approved in the EU for ATTR are the TTR tetramer stabilising agent tafamidis and the TTR silencing agents inotersen, patisiran, and vutrisiran (Table 2).

Table 2. Authorised Medicines for the Treatment of ATTR

Proprietary name	Generic name	Therapeutic indication	MAA approval date in EU
VYNDAQEL	Tafamidis	Treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (VYNDAQEL 20 mg soft capsules)	16 November 2011
		Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (VYNDAQEL 61 mg soft capsules)	
TEGSEDI	Inotersen	Treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)	06 July 2018
ONPATTRO	Patisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR)a in adult patients with Stage 1 or Stage 2 polyneuropathy	27 August 2018
AMVUTTRA	Vutrisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or Stage 2 polyneuropathy	15 September 2022

Since the initial orphan designation, new authorised treatments for ATTR amyloidosis have become available.

Among the currently authorized treatments for the condition, the only product for which a significant benefit comparison is required relative to Beyonttra is Vyndaqel (tafamidis). This is because Beyonttra specifically targets an overlapping patient population as Vydanqel—adult individuals with transthyretin amyloid cardiomyopathy (ATTR-CM), encompassing both wild-type and hereditary forms.

In contrast, the other approved therapies—Tegsedi, Onpattro, and Amvuttra—are indicated solely for the treatment of polyneuropathy in hereditary transthyretin amyloidosis. These products are not authorised for the treatment of ATTR-CM and, therefore, are not relevant comparators for the intended patient population of Beyonttra.

Significant benefit

The sponsor engaged with the European Medicines Agency (EMA) to obtain protocol assistance regarding the evidence required to demonstrate a significant benefit of Beyonttra over existing treatments for patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM), including both wild-type and hereditary forms. As part of this guidance, the Committee for Orphan Medicinal Products (COMP) recommended conducting a head-to-head clinical trial vis a vis tafamidis to establish significant benefit (EMEA/H/SA/4038/1/FU/1/2020/PA/III).

However, the sponsor clarified that, during the design, protocol finalisation, and early stages of participant enrolment for the ATTRibute-CM study, tafamidis was not yet widely available in the EU, also due limited reimbursement status (April 2019 to October 2020). Consequently, the sponsor opted to conduct the pivotal Phase 3 trial, ATTRibute-CM, as a placebo-controlled study instead. To compensate for the absence of a direct comparison with tafamidis, the sponsor performed an anchored Matching-Adjusted Indirect Comparison (MAIC) to evaluate the relative efficacy of acoramidis compared to tafamidis, in order to establish a Significant Benefit based on an advantage of efficacy.

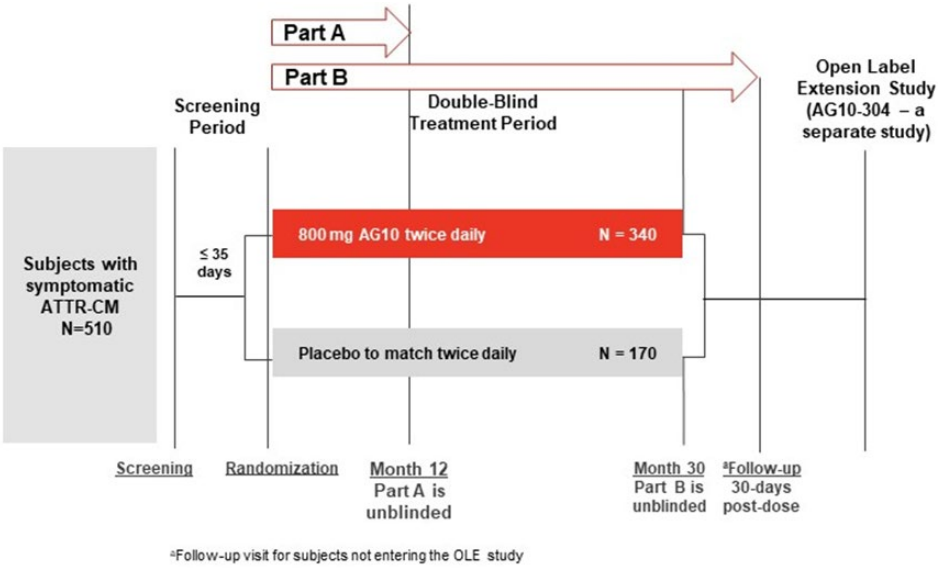
For the indirect comparison, data were used form the single pivotal trial, the ATTRibute-CM study, which aimed to assess the efficacy of acoramidis in managing symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) over a 30-month period. Eligible participants, aged 18-90 years, had a confirmed diagnosis of ATTR-CM (either wild-type or variant TTR genotype) and presented with New York Heart Association (NYHA) Class I-III heart failure symptoms. Further inclusion criteria required a 6-minute walk test (6MWT) distance of at least 150 meters, NT-proBNP levels between 300 and 8500 pg/mL, and a left ventricular wall thickness of at least 12 mm. Key exclusion criteria included light-chain amyloidosis, recent cardiac events (e.g., myocardial infarction within the past 90 days), and severe renal impairment (eGFR <15 mL/min/1.73 m^2).

In total 632 participants were randomized in a 2:1 ratio to receive either 800 mg of acoramidis twice daily or a matching placebo, with the option to add tafamidis after the initial 12 months if it became available locally. Treatment assignment was stratified by whether participants had ATTRv-CM or ATTRwt-CM, and baseline disease severity, based on NTproBNP level and renal function.

The primary endpoint was a hierarchical composite outcome that encompassed all-cause mortality, cardiovascular (CV)-related hospitalizations, changes in NT-proBNP levels, and 6MWT performance over the 30-month duration. Secondary endpoints included changes in 6MWT, Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, and serum transthyretin (TTR) levels, alongside all-cause mortality. The Schematic representation is displayed in Figure 1.

The sponsor claims that acoramidis offers a significant benefit over tafamidis for treating ATTR-CM based on a clinically relevant advantage regarding efficacy. Further comparative analyses were performed to establish the potential superiority of acoramidis, particularly in terms of overall survival, functional capacity, and biomarker improvements.

Figure 1. Study Schematic of ATTRibute-CM Trial:



Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; N = total number of participants in the study arm; OLE = open label extension

Matching-Adjusted Indirect Comparison (MAIC):

The sponsor conducted a detailed MAIC to evaluate the efficacy of acoramidis relative to tafamidis in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). This approach leveraged data from two pivotal Phase 3 studies: ATTRibute-CM for acoramidis and ATTR-ACT for tafamidis. The analysis aimed to provide comparative evidence on key clinical outcomes, specifically focusing on all-cause mortality (ACM) and cardiovascular-related hospitalizations (CVH).

The MAIC analysis utilized individual patient-level data from the ATTRibute-CM study for acoramidis, and aggregate data published from the ATTR-ACT study for tafamidis. The adjustment process was designed to align the baseline characteristics of the two patient cohorts, thereby aiming at enhancing comparability despite differences in study designs and patient demographics.

The sponsor indicates that the National Institute for Health and Care Excellence (NICE) guidelines recommend that, for an anchored approach in indirect comparisons, adjustments should focus on treatment effect modifiers rather than prognostic factors. Effect modifiers are variables that interact with treatment to influence outcomes, whereas prognostic factors are controlled through randomization within studies. Imbalances in prognostic variables are addressed by randomization, and including prognostic factors in the matching model would primarily reduce the effective sample size (ESS) without impacting the point estimates, thus potentially increasing uncertainty.

To identify appropriate effect modifiers, a multi-step process was employed. Initially, subgroup forest plots from both the ATTRibute-CM and ATTR-ACT trials were analysed to detect potential effect modification signals, particularly for key outcomes like all-cause mortality (ACM) and cardiovascular (CV)-related hospitalizations. Given that subgroup analyses often lack sufficient statistical power, clinical expert input was also sought.

Two external and one internal Key Opinion Leaders (KOLs) were consulted to evaluate whether specific baseline characteristics could be considered effect modifiers. The external KOLs independently completed detailed questionnaires, providing their assessments and ranking potential effect modifiers. Any differences in their responses were resolved through follow-up teleconferences. The internal KOL contributed insights but did not complete the formal questionnaire process.

All consulted KOLs unanimously agreed that NYHA class was a significant effect modifier, with patients classified as NYHA Class III likely to derive less benefit from treatment compared to those with lower NYHA classes. Other baseline characteristics were classified either as prognostic factors or as having no effect on treatment outcomes, emphasizing the focus on factors that directly interact with treatment efficacy.

For matching purposes, the full list of key effect modifiers identified for matching included:

- TTR genotype (wild-type vs. variant);
- New York Heart Association (NYHA) class;
- NT-proBNP levels;
- and Age.

A feasibility assessment confirmed that MAIC was suitable, given the differences in trial designs, patient characteristics, and available outcome data. This included adjustments for NT-proBNP levels and exclusion of patients with certain health conditions to balance baseline characteristics.

While the ATTRibute-CM and ATTR-ACT trials shared broadly similar designs (Table 3), there were notable temporal and contextual differences that could influence the comparability of their outcomes. The ATTRibute-CM trial was conducted seven years after ATTR-ACT, during which time advancements in supportive care and earlier disease diagnosis have been shown by Ioannou et al. 2022 to significantly enhance overall survival (OS). The sponsor therefore suggests that patients enrolled in the earlier ATTR-ACT trial may have had more advanced cardiac disease compared to those in the later ATTRibute-CM study. As a result, the improved management of the disease in more recent years may have potentially attenuated the relative treatment effect of acoramidis.

Additionally, while both trials measured outcomes over a 30-month period, there was a key difference in the use of concomitant therapies. In the ATTRibute-CM trial, the use of tafamidis was allowed after the first 12 months for participants in both the acoramidis and placebo groups. Notably, 14.5% of patients in the acoramidis arm and 21.8% in the placebo arm received concomitant tafamidis after month 12.

Table 3. Key Study Designs

Study Name	ATTRibute-CM (NCT03860935)	ATTR-ACT (NCT01994889)
Source	Protocol AG10-301 Amendment 5.0	Protocol B3461028 - 28 August 2018 - Final
Treatment Arms	Acoramidis HCl 800 mg vs. placebo (Overall N=632 at 05-August-2022)	Tafamidis 80 mg (N=176) vs. Tafamidis 20 mg (N=88) vs. placebo (N=177)
Study Design	RCT, Phase 3, double-blind, multinational (18), multicenter (approx. 130)	RCT, Phase 3, 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)** • **Estimated glomerular filtration rate (eGFR) (≥ 45 vs. < 45 mL/min/1.73 m²)**	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	09-December-2013/07-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
Analysis Population	• ITT population included: all randomized patients who received at least one dose of study medication and had at least one post baseline efficacy evaluation and excluding patients **with eGFR <15 mL/min/1.73 m²** at screening. • The modified ITT (mITT) population was used for primary analysis and it excluded patients **with eGFR <30 mL/min/1.73 m²** at screening. • For safety analysis all patients who received at least one dose of study medication were included.	• The ITT population included: all randomized patients who received at least one dose of study medication and had at least one post baseline efficacy evaluation and excluding patients **with eGFR <25 mL/min/1.73 m²** at screening. • The ITT population was used in the primary analysis. The mITT had the same definition as the ITT. • For safety analysis all patients who received at least one dose of study medication were included.
Key Primary Endpoints	**Part A:** CFB in 6MWT to Month 12 of treatment **Part B:** Hierarchical combination of all-cause mortality and cumulative frequency of CV-related hospitalizations, **change from baseline in the NT-proBNP**, and CFB in 6MWT over a 30-month period.	**Hierarchical combination all-cause mortality 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 all-cause mortality and CV-related hospitalization over a 30-month period** • **All-cause mortality, CV-related mortality, cumulative frequency of CV-related hospitalization by Month 30, and safety** Exploratory endpoints for Part A and B: • CFB in NT-proBNP/Troponin I/**EQ-5D-5L**. PK-PD analyses. Additional assays comparing acoramidis activity across a panel of TTR variants.	**CFB in 6MWT/KCCQ-OS to Month 30, all-cause mortality, CV-related mortality, frequency of CV-related hospitalization, TTR stabilization at Month 1, and safety** Exploratory: • **EQ-5D-3L**

6MWT = 6-Minute walk test; ATTR-CM = Transthyretin amyloid cardiomyopathy; CFB=Change from baseline; CV=Cardiovascular; eGFR=Estimated glomerular filtration rate; EQ-5D=EuroQol 5-dimension; HCl=Hydrochloride; ITT=Intent-to-treat; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary score; mITT = modified ITT; NT-proBNP = N-terminal pro-Brain-type Natriuretic Peptide; NYHA = New York Heart Association; PAIC = Population-adjusted indirect comparison; PK-PD = Pharmacokinetic-pharmacodynamic; RCT = Randomized clinical trial; TEAE = Treatment-emergent adverse event; TTR = Transthyretin

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As pointed out by the sponsor, there were notable differences in the **inclusion criteria** between the two trials:

1. Estimated Glomerular Filtration Rate (eGFR):
    - ATTRibute-CM excluded patients with eGFR <30 mL/min/1.73 m², while ATTR-ACT set the threshold at <25 mL/min/1.73 m².
    - The exclusion of patients with eGFR <25 mL/min/1.73 m² in the MAIC analysis was necessary to align the cohorts and reduce potential bias favouring acoramidis.
2. 6-Minute Walk Test (6MWT):
    a. ATTRibute-CM required a stricter 6MWT threshold (≥150 meters) compared to ATTR-ACT (>100 meters), potentially resulting in a healthier cohort in the acoramidis trial.
3. NT-proBNP Levels:
    a. ATTRibute-CM included patients with NT-proBNP levels between 300 and 8500 pg/mL, while ATTR-ACT had a lower bound of ≥600 pg/mL with no upper limit.
    b. To align with the ATTR-ACT criteria, patients with NT-proBNP <600 pg/mL in ATTRibute-CM were excluded from the analysis.
4. Modified Body Mass Index (mBMI):
    a. ATTR-ACT excluded patients with mBMI <600 kg/m²×g/L, while ATTRibute-CM did not have this restriction. Patients below this threshold in ATTRibute-CM were excluded to ensure comparability.

The **baseline characteristics** of patients in the ATTRibute-CM and ATTR-ACT trials were generally similar, but notable differences existed in specific demographics and clinical factors (Table 4):

- TTR Genotype: Fewer patients with variant ATTR were enrolled in ATTRibute-CM compared to ATTR-ACT.
- Heart Failure Severity: The proportion of NYHA Class III patients was lower in ATTRibute-CM, suggesting a less severely diseased population
- NT-proBNP Levels: Patients in ATTRibute-CM had lower baseline NT-proBNP levels, indicating less advanced cardiac dysfunction.
- Age and Medication Use: ATTRibute-CM included older patients and a higher prevalence of baseline medications, such as ACEi and beta-blockers, which are, according to the Sponsor, prognostic but not expected to impact treatment efficacy directly.

Overall, these differences suggest that the ATTRibute-CM population had a less advanced stage of disease than ATTR-ACT, likely due to earlier diagnosis and improved supportive care. These baseline discrepancies were addressed in the analysis to minimize potential biases in the indirect comparison of acoramidis and tafamidis.

Table 4. Baseline characteristics across trials.

Trial	ATTRibute-CM (ITT)			ATTR-ACT			Comparison
Treatment Arm	All Subjects (N=632)	Acoramidis (N=421)	Placebo (N=211)	Tafamidis (80 mg) (N=176)	Pooled Tafamidis (80 mg and 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)	**Different**
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)	**Different**
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)	**Different**
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)	2,867.0 (2,138.3)	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)	**Different**
Median (Min, Max)	2,325.5 (277, 15,711)	2326.0 (280, 15711)	2306.0 (277, 8829)	3,122 (392.0, 22,020.1)	2,995.9	3,161 (298.0, 16,787.1)	
Permanent pacemaker insert, n (%)							
Yes	91 (14.4)	69 (16.4)	22 (10.4)	NR	13 (4.9)	12 (6.8)	**Different**
No	541 (85.6)	352 (83.6)	189 (89.6)	NR	251 (95.1)	165 (93.2)	
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)	**Similar**

Trial	ATTRibute-CM (ITT)			ATTR-ACT			Comparison
Treatment Arm	All Subjects (N=632)	Acoramidis (N=421)	Placebo (N=211)	Tafamidis (80 mg) (N=176)	Pooled Tafamidis (80 mg and 20 mg) (N=264)	Placebo (N=177)	
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 (%)	21 (3.3)	12 (2.9)	9 (4.3)	16 (9.1)	27 (10.2)	15 (8.5)	
≥65, n (%)	611 (96.7)	409 (97.1)	202 (95.7)	160 (90.9)	237 (89.8)	162 (91.5)	
Sex, n (%)							
Male	570 (90.2)	384 (91.2)	186 (88.2)	158 (89.8)	241 (91.3)	157 (88.7)	**Similar**
Female	62 (9.8)	37 (8.8)	25 (11.8)	18 (10.2)	23 (8.7)	20 (11.3)	
Implanted cardiac defibrillator, n (%)							
Yes	24 (3.8)	12 (2.9)	12 (5.7)	NR	16 (6.1)	9 (5.1)	**Similar**
No	608 (96.2)	409 (97.1)	199 (94.3)	NR	248 (93.9)	168 (94.9)	
Ethnicity, n (%)							
Hispanic/ Latino	12 (1.9)	8 (1.9)	4 (1.9)	4 (2.3)	7 (2.7)	7 (4.0)	**Similar**
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)	**Similar**
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)	**Different**
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)	**Similar**

Trial	ATTRibute-CM (ITT)			ATTR-ACT			Comparison
Treatment Arm	All Subjects (N=632)	Acoramidis (N=421)	Placebo (N=211)	Tafamidis (80 mg) (N=176)	Pooled Tafamidis (80 mg and 20 mg) (N=264)	Placebo (N=177)	
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)	**Similar**
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)	**Similar**
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)	Different
Beta blockers	291 (46.0)	194 (46.1)	97 (46.0)	NA	76 (28.8)	53 (29.9)	Different
Diuretics	540 (85.4)	359 (85.3)	181 (85.8)	NA	175 (66.3)	123 (69.5)	Different
Antithrombotic agents	511 (80.9)	342 (81.2)	169 (80.1)	NA	105 (39.8)	72 (40.7)	Different

Abbreviations: 6MWT = 6-minute walk test; ATTR = transthyretin amyloid; ATTR-ACT=Transthyretin Cardiomyopathy Clinical ; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary transthyretin amyloidosis; ATTRwt = wild-type ATTR; BMI = body mass index; ITT=Intent to treat; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; SD = Standard deviation; TBD = to be determined;

*The mean and standard deviation of the pooled tafamidis (80 mg and 20 mg) data were not reported in the publications. The pooled mean was obtained by multiplying the means of tafamidis (80 mg) and tafamidis (20 mg) by their respective sample sizes and then dividing the sum by the total number of samples. The pooled standard deviation was calculated by applying a weighted average method that considered the sample sizes and standard deviations of each dose group.[18]

**The modified BMI is calculated by multiplying the BMI by the serum albumin concentration (g/L).

***Overall Summary is the mean of the Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation scores.

****Clinical Summary is the mean of the Physical Limitation, Symptom Frequency, and Symptom Burden scores

The main outcomes evaluated in the MAIC were all-cause mortality (ACM)hazard ratio (HR) over 30 months, and relative risk ratio (RRR) of cardiovascular (CV)-related hospitalizations. The definition of CVH was aligned between studies, excluding certain events to maintain consistency.

To address these imbalances, the sponsor evaluated four distinct MAIC scenarios:

Scenario 1: Excluded patients with low eGFR and NT-proBNP, adjusting for transthyretin (TTR) genotype, New York Heart Association (NYHA) class, and NT-proBNP.

Scenario 2: Similar exclusions but adjusted only for NYHA class and NT-proBNP, omitting TTR genotype.

Scenario 3 (Base-Case): Excluded the same patients and adjusted for all key effect modifiers: TTR genotype, NYHA class, NT-proBNP, and age.

Scenario 4: Adjusted all modifiers in Scenario 3 but without excluding patients with low eGFR, as suggested to offset differences in NT-proBNP eligibility between trials.

Scenario 3 was chosen as the base-case analysis due to its comprehensive adjustments, aligning with NICE guidelines, according to the sponsors' argumentation. To account for the potential confounding impact of concomitant tafamidis use, data from participants who received tafamidis after month 12 were excluded. Additionally, sensitivity analyses were performed to include all participants, irrespective of concomitant tafamidis use.

Results

In the comparative analysis of baseline characteristics between the ATTRibute-CM and ATTR-ACT trials, several differences between the two study populations were identified. Notable variations included a lower prevalence of patients with variant (mutant) ATTR, a smaller proportion of individuals in New York Heart Association (NYHA) Class III, and lower NT-proBNP levels within the ATTRibute-CM cohort. These discrepancies were addressed using the MAIC approach across four different scenarios. Baseline characteristics considered primarily as prognostic factors—such as permanent pacemaker use and specific medications (e.g., diuretics, beta-blockers)—were claimed to have remained relatively balanced between trials (Table 5).

Table 5. Baseline Characteristics Before and After Matching ATTRibute-CM to ATTR-ACT, ITT Population

	ATTRibute-CM										ATTR-ACT	
	Acoramidis Unmatched (N=421)	Acoramidis Matched Scenario 1 (ESS=242.2)	Acoramidis Matched Scenario 2 (ESS=311.3)	Acoramidis Matched Scenario 3 (ESS=208.7)	Acoramidis Matched Scenario 4 (ESS=218.7)	Placebo Unmatched (N=211)	Placebo Matched Scenario 1 (ESS=102.7)	Placebo Matched Scenario 2 (ESS=121.7)	Placebo Matched Scenario 3 (ESS=88.7)	Placebo Matched Scenario 4 (ESS=89)	Tafamidis (N=176)	Placebo (N=177)
TTR Genotype, n (%)												
ATTRv	41 (9.7)	**23.9**	8.2	**23.9**	**23.9**	20 (9.5)	**24.3**	9.2	**24.3**	**24.3**	**42 (23.9)**	**43 (24.3)**
ATTRwt	380 (90.3)	**76.1**	91.8	**76.1**	**76.1**	191 (90.5)	**75.7**	90.8	**75.7**	**75.7**	**134 (76.1)**	**134 (75.7)**
NYHA Class, n (%)												
I	51 (12.1)	**9.1**	**9.1**	**9.1**	**9.1**	17 (8.1)	**7.3**	**7.3**	**7.3**	**7.3**	**16 (9.1)**	**13 (7.3)**
II	293 (69.6)	**59.7**	**59.7**	**59.7**	**59.7**	162 (76.8)	**57.1**	**57.1**	**57.1**	**57.1**	**105 (59.7)**	**101 (57.1)**
III	77 (18.3)	**31.2**	**31.2**	**31.2**	**31.2**	32 (15.2)	**35.6**	**35.6**	**35.6**	**35.6**	**55 (31.3)**	**63 (35.6)**
Race, n (%)												
Black	20 (4.8)	9.4	3.9	10.7	11	10 (4.7)	9.2	3.8	9.5	9.5	26 (14.8)	26 (14.7)
White	368 (87.4)	80.2	87.7	80.4	80.4	187 (88.6)	82.6	89.1	80.4	79.7	136 (77.3)	146 (82.5)
Asian	10 (2.4)	2.7	2.1	2.5	2.4	3 (1.4)	0.3	0.4	0.2	0.8	11 (6.3)	5 (2.8)
Other	7 (1.7)	3.8	1.7	3	2.9	3 (1.4)	4.3	2.7	5.5	5.6	3 (1.7)	0
Not Reported	16 (3.8)	3.9	4.6	3.4	3.4	8 (3.8)	3.6	4	4.4	4.4	0	0
Ethnicity, n (%)												
Hispanic/Latino	8 (1.9)	2.6	2.1	2.8	2.7	4 (1.9)	1.4	1.2	1.9	1.9	4 (2.3)	7 (4.0)
Not Hispanic/Latino	401 (95.2)	93.9	94	94.2	94.3	199 (94.3)	95.5	94.9	94.7	94.7	171 (97.2)	170 (96.0)
Not Reported/Unknown	12 (2.9)	3.4	3.9	3	2.9	8 (3.8)	3.1	3.9	3.4	3.4	1 (0.6)	0
NT-proBNP (ng/ml)												
Mean (SD)	2.9 (2.2)	**3.9 (2.2)**	**3.9 (2.5)**	**3.9 (2.1)**	**3.9 (2.1)**	2.7 (2.0)	**3.8 (1.6)**	**3.8 (1.8)**	**3.8 (1.6)**	**3.8 (1.6)**	**3.9 (3.1)**	**3.8 (3.0)**
Median (Min, Max)	2.3 (0.3, 15.7)	**3.1 (0.4, 15.7)**	**3.1 (0.4, 15.7)**	**3.1 (0.4, 15.7)**	**3.1 (0.4, 15.7)**	2.3 (0.3, 8.8)	**3.2 (0.5, 8.8)**	**3.2 (0.5, 8.8)**	**3.2 (0.5, 8.8)**	**3.2 (0.5, 8.8)**	**3.1 (0.4, 22.0)**	**3.2 (0.3, 16.8)**

	ATTRibute-CM										ATTR-ACT	
	Acoramidis Unmatched (N=421)	Acoramidis Matched Scenario 1 (ESS=242.2)	Acoramidis Matched Scenario 2 (ESS=311.3)	Acoramidis Matched Scenario 3 (ESS=208.7)	Acoramidis Matched Scenario 4 (ESS=218.7)	Placebo Unmatched (N=211)	Placebo Matched Scenario 1 (ESS=102.7)	Placebo Matched Scenario 2 (ESS=121.7)	Placebo Matched Scenario 3 (ESS=88.7)	Placebo Matched Scenario 4 (ESS=89)	Tafamidis (N=176)	Placebo (N=177)
Sex, n (%)												
Male	384 (91.2)	90.7	91.8	91.5	91	186 (88.2)	84.8	86.1	88	88	158 (89.8)	157 (88.7)
Age (years)												
Mean (SD)	77.4 (6.5)	77.4 (5.1)	78.0 (5.6)	75.5 (5.4)	75.5 (5.4)	77.1 (6.8)	77.0 (5.5)	78.2 (5.4)	75.0 (5.1)	75.0 (5.1)	75.2 (7.2)	74.1 (6.7)
Median (Min, Max)	78.0 (50, 91)	78.0 (50, 91)	78.9 (50, 91)	**76.0 (50, 88)**	**76.0 (50, 88)**	78.0 (55, 91)	78.0 (55, 91)	79.0 (55, 91)	**74.5 (55, 89)**	**74.5 (55, 89)**	**76.0 (46, 88)**	**74.0 (51, 89)**
<65 years, n (%)	12 (2.9)	3.5	2.2	**9.1**	**9.1**	9 (4.3)	7.5	3.8	**8.5**	**8.5**	**16 (9.1)**	**15 (8.5)**
≥65 years, n (%)	409 (97.1)	96.5	97.8	**90.9**	**90.9**	202 (95.7)	92.5	96.2	**91.5**	**91.5**	**160 (90.9)**	**162(91.5)**
BMI												
Mean (SD)	27.07 (3.793)	26.78 (3.070)	26.88 (3.350)	26.93 (2.939)	26.95 (2.967)	27.01 (3.766)	26.17 (2.581)	26.39 (2.860)	26.25 (2.526)	26.23 (2.509)	26.32 (3.805)	26.33 (4.277)
Min, Max	18, 43	18, 43	18, 43	18, 43	18, 43	19, 40	19, 40	19, 40	19, 40	19, 40	18, 40	16, 48
Duration (years) of ATTR-CM												
Mean (SD)	1.24 (1.203)	1.37 (1.093)	1.35 (1.261)	1.40 (1.046)	1.40 (1.032)	1.12 (1.195)	1.34 (0.864)	1.31 (0.975)	1.39 (0.818)	1.40 (0.813)	0.93 (1.179)	1.23 (1.439)
Median (Min, Max)	0.84 (0.0, 10.1)	0.96 (0.0, 10.1)	0.91 (0.0, 10.1)	0.98 (0.0, 10.1)	0.99 (0.0, 10.1)	0.71 (0.0, 7.4)	0.91 (0.0, 5.1)	0.83 (0.0, 5.1)	1.01 (0.0, 5.1)	1.02 (0.0, 5.1)	0.56 (0.0, 6.9)	0.67 (0.0, 7.9)
Permanent Pacemaker, n (%)												
Yes	81 (19.2)	23.4	22.8	20.5	19.7	39 (18.5)	17.1	19.7	18.8	18.6	13 (4.9)†	12 (6.8)
Implanted Cardiac Defibrillator, n (%)												
Yes	26 (6.2)	6.4	6.7	7	6.8	17 (8.1)	8.5	8.5	9.2	9.1	16 (6.1)†	9 (5.1)
6MWT												

	ATTRibute-CM										ATTR-ACT	
	Acoramidis Unmatched (N=421)	Acoramidis Matched Scenario 1 (ESS=242.2)	Acoramidis Matched Scenario 2 (ESS=311.3)	Acoramidis Matched Scenario 3 (ESS=208.7)	Acoramidis Matched Scenario 4 (ESS=218.7)	Placebo Unmatched (N=211)	Placebo Matched Scenario 1 (ESS=102.7)	Placebo Matched Scenario 2 (ESS=121.7)	Placebo Matched Scenario 3 (ESS=88.7)	Placebo Matched Scenario 4 (ESS=89)	Tafamidis (N=176)	Placebo (N=177)
Mean (SD)	361.21 (103.705)	340.73 (78.106)	341.75 (90.094)	348.86 (74.552)	348.45 (76.575)	348.37 (93.564)	318.22 (70.970)	315.03 (77.386)	325.25 (69.837)	326.49 (71.125)	350.55 (121.296)†	353.26 (125.983)
Median (Min, Max)	363 (151, 696)	335 (159, 696)	336 (159, 696)	342 (159, 696)	342 (151, 696)	349 (151, 598)	328 (151, 560)	317 (151, 560)	338 (151, 560)	338 (151, 598)	342.5 (61, 685)	346 (80, 822)
KCCQ-OS – overall summary score												
Mean (SD)	71.52 (19.39)	67.27 (15.79)	68.15 (18.05)	66.53 (15.10)	66.45 (15.38)	70.31 (20.54)	63.20 (16.83)	64.13 (17.70)	62.04 (15.47)	61.96 (15.38)	67.28 (21.36)†	65.90 (21.74)
Use of Diuretics, n (%)												
Yes	359 (85.3)	90.1	89.6	89	89.1	181 (85.8)	88.2	90.3	88.4	88.6	175 (66.3)†	123 (69.5)
Use of Antithrombotic Agents, n (%)												
Yes	342 (81.2)	83.1	83.9	83	83.4	169 (80.1)	81	84.8	78.9	78.9	105 (39.8)†	72 (40.7)
Use of Agents Acting on the Renin-angiotensin System, n (%)												
Yes	188 (44.7)	45.1	43.3	43.5	44.1	88 (41.7)	40.3	39.9	42.3	42	69 (26.1)†	48 (27.1)
Use of Beta-blockers, n (%)												
Yes	194 (46.1)	50.7	49.2	52.4	50.9	97 (46.0)	51.4	48.6	53.8	53.7	76 (28.8)†	53 (29.9)

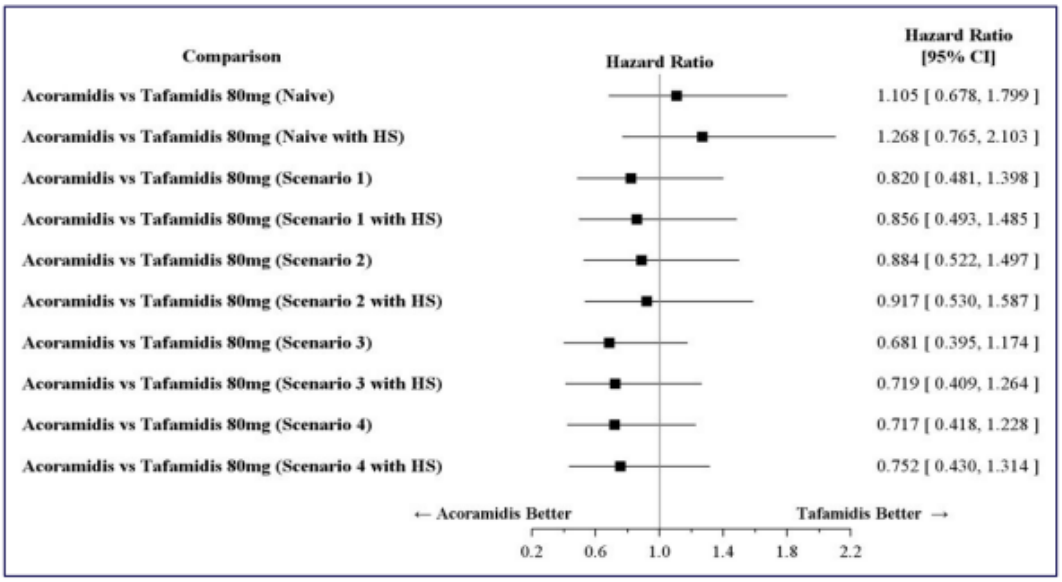
Abbreviations: 6MWT = six-minute walk test; ATTR-ACT=Transthyretin Cardiomyopathy Clinical; ATTRv = hereditary transthyretin amyloidosis; ATTRwt = wild-type; BMI = body mass index; ESS = effective sample size; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = Ney York Heart Association; SD = standard deviation; TTR = transthyretin;
† Reported for the pooled tafamidis (80 mg and 20 mg). Denominator is 264. **Bold** characteristics were matched.

In the most comprehensive scenario according to the sponsor (Scenario 3), where matching was conducted on all relevant effect modifiers, including estimated glomerular filtration rate (eGFR), NT-proBNP levels, NYHA class, TTR genotype, and age, the effective sample size (ESS) was notably reduced. The ESS decreased by approximately 50% in the acoramidis arm and 58% in the placebo arm, reflecting the redistribution of patient weights to enhance comparability. The weight distribution showed a skewed pattern, with some patients being assigned weights up to 7.7 times their original,

unadjusted value, and a large proportion under the value of 1 specially for the placebo arm. Scenarios that involved fewer adjustments exhibited less reduction in ESS.

Regarding ACM, the initial unadjusted analysis suggested a slightly higher, albeit statistically nonsignificant, risk of death with acoramidis compared to tafamidis (Hazard Ratio [HR]: 1.105; 95% CI: 0.678–1.799). However, after applying Scenario 3 adjustments and using a hypothetical strategy to account for patients who received concomitant tafamidis, the adjusted hazard ratio indicated a trend towards improved survival with acoramidis (HR: 0.719; 95% CI: 0.409–1.264), corresponding to a 28% relative reduction in death risk, though still without reaching statistical significance. This indicated the high impact of the effect modifiers of choice. Across all four MAIC scenarios, the trend remained consistent, with point estimates for ACM ranging from 0.681 to 0.917, suggesting a general trend toward improved survival with acoramidis, albeit point estimates were not homogeneous (Figure 2).

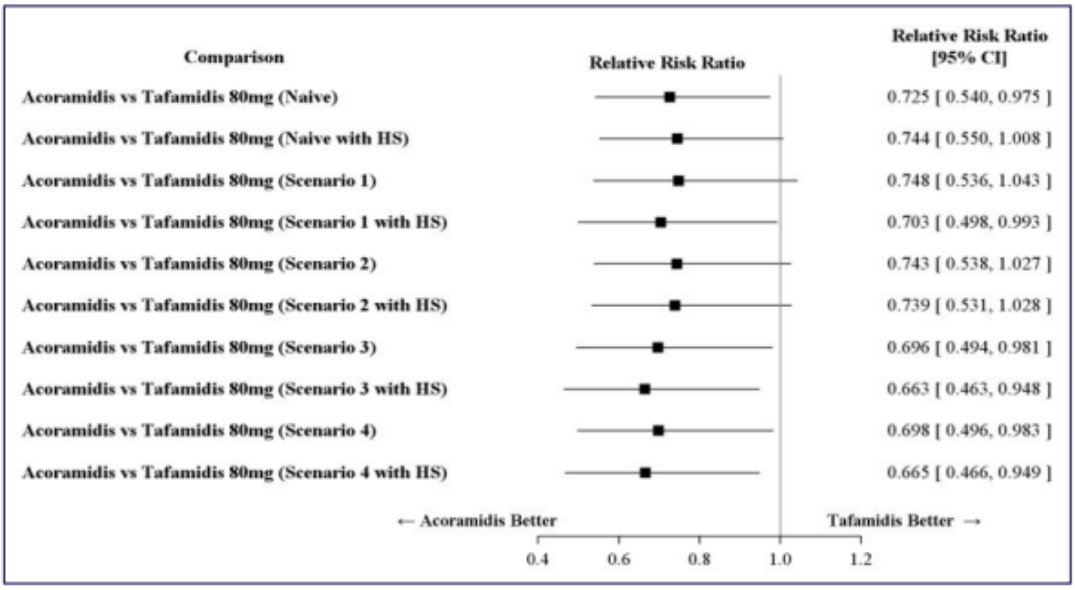
Figure 2. ACM in the ITT Population



Abbreviations: CI = confidence interval; HS = hypothetical strategy
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
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
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age

In the evaluation of cardiovascular-related hospitalizations, excluding Events of Clinical Interest (EOCIs) to align with the definitions used in the ATTR-ACT trial, the unadjusted analysis demonstrated a significant reduction in hospitalization risk favouring acoramidis (Relative Risk Reduction [RRR]: 0.725; 95% CI: 0.540–0.975). Scenario 3, adjusted with the hypothetical strategy, further supported this reduction (RRR: 0.663; 95% CI: 0.463–0.948), translating to a 34% lower risk of cardiovascular-related hospitalizations with acoramidis. Other scenarios produced a similar trend in findings (Figure 3).

Figure 3. Cumulative Frequency of CV-related Hospitalization Excluding ECOIs in the ITT Population.



Abbreviations: CI = confidence interval; HS = hypothetical strategy
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
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
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age

Overall, the adjustments and subsequent analyses in this study provide a comprehensive comparison, supporting a trend toward improved survival and significantly lower cardiovascular hospitalization rates with acoramidis relative to tafamidis, albeit with non-significant findings in survival metrics across scenarios. However, the COMP is of the opinion that the current analysis presents several potential limitations that could impact the robustness and generalizability of the findings due to a potential high level of uncertainty on the results presented and required further clarification.

One key limitation is the substantial reduction in the effective sample size (ESS), particularly in the scenario of choice, Scenario 3 (with reductions of 50% for the acoramidis arm and 58% for the placebo arm). This ESS reduction can undermine the generalisability of the findings, it highlights the lack of overlap across the study populations, and it will increase uncertainty, specifically in such a general efficacy endpoint such as all-cause mortality, that is associated with high variability and more prone to wider confidence intervals. Additionally, while the selection of covariates for matching was guided by expert opinion, it lacked a quantitative rationale or clear justification for why certain factors were included or excluded, particularly those deemed prognostic. This approach may introduce bias, as the exclusion of relevant variables in the matching could potentially distort the estimated treatment effects and potentially skew the treatment effect estimates. Notably, the decision not to include concomitant medication as effect modifiers, despite differing rates of use between trials, raises concerns. Clarification on this choice and its implications would strengthen the validity of the results.

The analysis further excluded data collected after patients in the acoramidis group began tafamidis treatment, using a hypothetical strategy intended to minimize confounding. However, this exclusion could introduce selection bias by omitting outcomes from patients who required additional therapy, potentially leading to an overestimation of acoramidis's efficacy. Providing insights into the outcomes for this specific patient subgroup would be valuable.

Differences in eligibility criteria as pointed out by the sponsor between the ATTRibute-CM and ATTR-ACT trials, such as varying NT-proBNP thresholds and eGFR cutoffs, may also affect the comparability of results, potentially limiting the generalizability of the findings to broader clinical practice. The variability in results across different scenarios suggests sensitivity to the choice of effect modifiers, highlighting the need for justification on the choice of these variables. The reported hazard ratios (HRs) and relative risk ratios (RRRs) are presented with large confidence intervals, especially in the survival analysis. Additional reporting of the clinical impact of these estimates (such as absolute risk reductions) could provide a clearer perspective on their potential clinical relevance. Kaplan-Meier plots including the naive and adjusted curved could also provide useful insights that go beyond the reporting of a single number (i.e. HR).

Addressing these limitations through more detailed sensitivity analyses, particularly regarding the handling of concomitant tafamidis use, and considering data-driven methods for identifying effect modifiers, would significantly enhance the reliability and interpretability of the study's conclusions.

4. COMP list of issues

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should justify the inclusion and choice of sources selected for the prevalence estimation and describe the methodology used for these calculations. The sponsor should consider recently published studies, particularly those reflecting increased prevalence rates following advancements in scintigraphy use, as these provide more direct and updated prevalence calculations.

Due to significant uncertainties surrounding many of the underlying assumptions, the sponsor should elaborate on the prevalence estimate for the proposed orphan condition. This recalculation should be grounded in up-to-date and relevant epidemiological studies and registries that accurately reflect the target population. Furthermore, the sponsor is asked to conduct a sensitivity analysis to assess the potential impact of these assumptions on the prevalence estimate. This analysis should consider variability across demographic factors such as age groups, particularly those that may disproportionately contribute to an over- or underestimation. Emphasis should be placed on data sources that align with current diagnostic practices to ensure a more reliable and representative estimate.

- Significant benefit

The sponsor is invited to clarify key methodological and analytical aspects of the indirect comparison between acoramidis and tafamidis, focusing on endpoint alignment, study population criteria, and outcome interpretation.

Specifically, the sponsor should address the comparability of primary endpoints between the trials, variations in study population criteria, and the processes used for matching. Additionally, the sponsor should provide clarification on the indirect comparison results, including the scientific rationale behind the Hypothetical Strategy and choice of matching variables (on individual basis), the implications of reduced Effective Sample Size (ESS) and skewed weight distributions, and the interpretation of confidence intervals and hazard ratios in light of any observed heterogeneity. In addition, the sponsor is invited to provide arguments on why baseline medication was not adjusted. Given the influence of

the background medication on the endpoints compared, the sponsor should discuss any potential imbalances that these could cause on the effect observed.