12 December 2024
EMA/66885/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Beyonttra

International non-proprietary name: acoramidis

Procedure No. EMEA/H/C/006333/0000

Note

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

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Administrative information

Name of the medicinal product:	Beyonttra
Applicant:	BridgeBio Europe B.V. Weerdestein 97 1083 GG Amsterdam NETHERLANDS
Active substance:	acoramidis hydrochloride
International Non-proprietary Name/Common Name:	acoramidis
Pharmaco-therapeutic group (ATC Code):	other cardiac preparations, other cardiac preparations
Therapeutic indication(s):	Beyonttra is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	356 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PCTFE/alu)
Package size(s):	120 tablets

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List of abbreviations

A25S	Variant with substitution of serine for alanine at amino acid 25 of transthyretin protein
A36D	Variant with substitution of aspartic acid for alanine at amino acid 36 of transthyretin protein
A97S	Variant with substitution of serine for alanine at amino acid 97 of transthyretin protein
Acoramidis-AG	Acoramidis acylglucuronide/-β-D-glucuronide
ADME	Absorption, distribution, metabolism, and excretion
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin amyloid polyneuropathy
ATTRv	Variant transthyretin amyloidosis
ATTRv-CM	Variant transthyretin amyloid cardiomyopathy
ATTRwt	Wild-type transthyretin amyloidosis
ATTRwt-CM	Wild-type transthyretin amyloid cardiomyopathy
AUC	Area under the curve
BE	Human bioequivalence
C_{max}	Maximum concentration
CMAs	Critical material attributes
CNS	Central nervous system
COX	Cyclooxygenase
CoC	Certificate of conformance
CPP	Critical process parameter
CQA	Critical quality attribute
CTD	Common technical document
CTM	Clinical trial material
D38A	Variant with substitution of alanine for aspartic acid at amino acid 38 of transthyretin protein
DMSO	Dimethyl sulfoxide
DMF	N,N-dimethylformamide / dimethylformamide
DoE/DOE	Design of experiments
DSC	Differential scanning calorimetry
DSp	Design space
DVS	Dynamic vapour sorption
E42D	Variant with substitution of aspartic acid for glutamic acid at amino acid 42 of transthyretin protein
E89Q	Variant with substitution of glutamine for glutamic acid at amino acid 89 of transthyretin protein
E92Q	Variant with substitution of glutamine for glutamic acid at amino acid 92 of transthyretin protein
ECG	Electrocardiography

EDTA	Ethylenediaminetetraacetic acid
Equiv	Molar equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
EU	European Union
F64L	Variant with substitution of leucine for phenylalanine at amino acid 64 of transthyretin protein
FITC	Fluorescein isothiocyanate
FLAG- tag	Peptide tag added to protein for multiple capture and detection applications
FP	Fluorescence polarisation
FPE	Fluorescent probe exclusion
FTIR	Fourier-transform infrared spectroscopy
G6S	Variant with substitution of serin for glycine at amino acid 6 of transthyretin protein
GC	Gas chromatography
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
hERG	Human ether-à-go-go-related gene
HBr	Hydrobromic acid
HDPE	High-density polyethylene
HPLC	High pressure liquid chromatography
I68L	Variant with substitution of leucine for isoleucine at amino acid 68 of transthyretin protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Us
ICP	Immune correlate of protection
IgG	Immunoglobulin
INN	International non-proprietary name
IPAc	Isopropyl acetate
IR	Infrared
ITC	Isothermal titration calorimetry
JP	Japanese Pharmacopoeia
JPE	Japanese pharmaceutical excipients
KCl	Potassium chloride
L58H	Variant with substitution of histidine for leucine at amino acid 58 of Transthyretin protein
LA/mUC	Locally advanced or metastatic urothelial cancer
LC	Liquid chromatography
LDPE	Low-density polyethylene
LOD	Limit of detection
LOQ	Limit of quantitation

Lys	Lysine
Met	Methionine
MDD	Maximum daily dose
MeOH	Methanol
MIs	Mutagenic impurities
MO	Major objection
MS	Mass spectrometry
MSD	Microscale thermophoresis
MST	Microscale thermophoresis
MTBE	Methyl tert-butyl ether / tert-Butylmethylether
NLT	Not less than
NMT	Not more than
NOEL	No observed effect level
OFAT	One-factor-at-a-time
OR	Operating ranges
OVIs	Organic volatile impurities
P24S	Variant with substitution of serine for proline at amino acid 24 of transthyretin protein
PAR	Proven acceptable range
PBS	Phosphate buffered saline
PD	Pharmacodynamics
pCPPs	Potential critical process parameters
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PMIs	Potentially mutagenic impurities
PSB	Primary stability batches
PVC	Polyvinyl chloride
PVdC	Polyvinyl chloride/polyvinylidene chloride
PXRD	Powder X-ray diffraction
QP	Qualified person
QRA	Quality risk assessment
(Q)SAR	(Quantitative) structure activity relationship
QTPP	Quality target product profile
QT interval	The portion of an electrocardiogram between the onset of the Q wave and the end of the T wave (representing ventricular repolarisation)
QTc	Corrected QT interval
RBP	Retinol binding protein also called RBP4
ROI	Residue on ignition

RSD	Relative standard deviation
S50R	Variant with substitution of arginine for serine at amino acid 50 of transthyretin protein
SCU	Stratified content uniformity
SCXRD	Single crystal X-ray diffraction
SDS	Sodium dodecyl sulfate
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
Ser	Serine
SPR	Surface plasmon resonance
T4	Thyroxine
T60A	Variant with substitution of alanine for threonine at amino acid 60 of transthyretin protein
T119M	Variant with substitution of methionine for threonine at amino acid 119 of transthyretin protein
TAMC	Total aerobic microbial count
TBM	To-be-marketed
TMS	Tetramethylsilane
TPF	Theoretical purge factor
TYMC	Total yeasts and moulds count
TTR	Transthyretin
TTRv	Transthyretin variant
TTRwt	Transthyretin wild type
Tyr	Tyrosine
UCSF	University of California San Francisco
UPLC-MS/MS	Ultra performance liquid chromatography-tandem mass spectrometry
USAN	United States adopted name
USP	United States Pharmacopoeia
USP-NF	United States Pharmacopeia-National Formulary
UV	Ultraviolet
V94L	Variant with substitution of leucine for valine at amino acid 94 of transthyretin protein
V122I	Variant with substitution of isoleucine for valine at amino acid 122 of transthyretin protein
V30M	Variant with substitution of methionine for valine at amino acid 30 of transthyretin protein
WB	Western blot
WT	Wild type
Y114C	Variant with substitution of cysteine for tyrosine at amino acid 114 of transthyretin protein
^{13}C-NMR	Carbon nuclear magnetic resonance spectroscopy
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy

XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BridgeBio Europe B.V. submitted on 7 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Beyonttra, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2023.

Beyonttra, was designated as an orphan medicinal product EU/3/18/2081 on 19 November 2018 in the following condition: Treatment of ATTR amyloidosis. The applicant requested the removal from the Community Register of Orphan Medicinal products on 5 December 2024.

The applicant applied for the following indication: Beyonttra is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0330/2018 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 12 December 2024. More information on the COMP's review can be found in the orphan withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Beyonttra.

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance acoramidis contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 March 2019	EMEA/H/SA/4038/1/2019/PA/III	Minne Casteels, Mogens Westergaard
26 April 2019	EMEA/H/SA/4038/2/2019/PA/II	Audrey Sultana, Nicolas Beix
29 January 2021	EMEA/H/SA/4038/1/FU/1/2020/PA/III	Clemens Mittmann, Mogens Westergaard
07 February 2022	EMA/SA/0000082236	Peter Mol, Finbarr Leacy

The protocol assistance pertained to the following quality, non-clinical and clinical aspects:

EMEA/H/SA/4038/1/2019/PA/III - Non-clinical and clinical development

- The approach for submission of carcinogenicity studies for MAA; agreement that no clinical drug-drug interaction (DDI) studies with CYP substrate(s)/inhibitor(s) and UDP-glucuronosyltransferase (UGT) substrate(s)/inhibitor(s)are required; the approach to define the need for a clinical AG10-OAT1/OAT3 DDI study.
- The overall design of the proposed single Phase 3 study (AG10-301) including the primary endpoint, approach for blinding, statistical analysis, population, dose; the proposed safety database; agreement with the plan not to conduct studies in renally or hepatically impaired populations; adequacy of the proposed cardiac monitoring to support a waiver of a thorough QT/QTc (TQT) study.

EMEA/H/SA/4038/2/2019/PA/II - Quality and non-clinical development

- The proposed specifications for AG10 HCl drug substance for use in the Phase 3 clinical trial; the proposed compounds as starting materials for GMP synthesis; the proposed specification for the 400 mg strength tablet for release of Phase 3 clinical trial investigational materials; the proposed limits for controlling two mutagenic impurities in AG10 drug substance during the Phase 3 study.

EMEA/H/SA/4038/1/FU/1/2020/PA/III - Non-clinical and clinical development

- Adequacy of the nonclinical and clinical pharmacology package to support a MAA in ATTR-CM.
- The approach to characterise the QTc prolongation potential of acoramidis.

- The statistical analysis plan for Part A of study AG10-301; the proposed measures for maintaining the blind in Part B of the ongoing Phase 3 ATTR-CM study; the proposed change in the Part B primary endpoint.
- Appropriateness of the implemented COVID-19-related modifications to study AG10-301; the plan to allow remote 6MWT to minimise missing data during COVID-19 measures.
- The approach for not reporting cardiovascular (CV)-related hospitalisation (CVH) as a suspected unexpected serious adverse event (SUSAR).

EMA/SA/0000082236 - Clinical development

- The proposed revision of the analytical approach of the Part B hierarchical composite endpoint of the ongoing Study AG10-301 to include changes in concomitant diuretic use and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: Janet Koenig

The application was received by the EMA on	7 January 2024
The procedure started on	1 February 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	30 April 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	8 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the List of Questions to all CHMP and PRAC members on	01 October 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2024
The CHMP agreed on a list of outstanding issues in writing and/or in to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the List of Outstanding Issues to	28 November 2024

all CHMP and PRAC members on	
The CHMP, in light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Beyonttra	12 December 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease resulting from the deposition of misfolded TTR as amyloid fibrils in various organs, predominantly the nerves and heart. The most clinically important manifestations are the result of involvement of the peripheral nervous system and the heart. Accumulation of amyloid fibrils in the heart causes an infiltrative, restrictive cardiomyopathy (ATTR-CM) resulting in progressive clinical heart failure associated with high mortality and morbidity. Patients with ATTR-CM typically experience frequent hospitalisations for heart failure, irreversible loss of physical function, and worsening health status and QoL. Advanced ATTR-CM causes some of the most deleterious adverse clinical outcomes in ATTR

2.1.2. Epidemiology and risk factors, screening tools/prevention

Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is thought to be present in over 40,000 persons worldwide. The prevalence of wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) has been more difficult to estimate accurately but is increasing, due to an evolving diagnostic landscape (including enhanced disease awareness and the broadening availability of a non-invasive diagnostic algorithm). Recent estimates found ATTR-CM to be the aetiology in up to 13% of an otherwise unselected population of patients presenting with heart failure and preserved ejection fraction.

2.1.3. Biologic features, aetiology and pathogenesis

The mechanisms underlying the pathophysiology of ATTRwt and its association with aging are currently poorly understood. In contrast, for ATTRv, more than 120 intrinsically destabilising TTR gene variants have been identified that are transmitted in an autosomal dominant fashion. V122I is the most common pathogenic variant found in the United Kingdom (UK) and in the United States (US), affecting 3% to 4% of people of African Caribbean descent, with a variable documented penetrance and clinical expressivity. The V30M pathogenic variant was the first to be described and is most commonly found in three geographic locations demonstrating a founder effect. The clinical syndrome associated with the early onset V30M variant was initially described in Portugal in 1952 as familial amyloid polyneuropathy, and subsequently in unrelated populations in Northeastern Sweden and Southwestern Japan, where the V30M variant displays an older age of disease onset than in Portugal. Also first described in Portugal was a highly stabilising (~37-fold more stable than wild type) variant (T119M) that protects V30M carriers (compound heterozygotes) from either developing or progressing the otherwise rapidly progressive polyneuropathy associated with V30M carriage.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Patients diagnosed with ATTR-CM tend to be male, on average 60 years old or older, and present with heart failure with preserved ejection fraction, often with cardiac conduction abnormalities (varying degrees of heart block) on an electrocardiogram (ECG), along with thickened ventricular walls, and evidence of diastolic dysfunction on echocardiogram. In addition, a carefully taken medical history

might reveal prior bilateral carpal tunnel syndrome (without predisposing risk factors for that condition) or lumbar spinal stenosis in the prior 5 to 10 years.

Until recently, ATTR-CM was underdiagnosed due to non-specific signs and symptoms often mistakenly attributed to more common conditions and the need to perform an endomyocardial biopsy for specific diagnostic confirmation in the absence of any available treatment. However, the past 10 years have borne witness to a profound transformation of the disease landscape due to several critical advances: (1) diagnostic confirmation is now possible by non-invasive means including scintigraphy (with bone radiotracers) coupled with the exclusion of a monoclonal gammopathy consistent with amyloid light chain (AL) amyloidosis by serum and urine protein biochemistry; (2) a widespread, global engagement by professional societies, and advocacy organisations to raise awareness among cardiologists and the broader medical community has driven increasingly earlier recognition and diagnosis. Disease awareness has been driven in part by the recognition of so-called red flags, like a history of bilateral carpal tunnel syndrome, leading to an earlier diagnosis and subsequent treatment than was previously achieved. The availability of an approved treatment, tafamidis, that was shown to reduce mortality and CV-related hospitalisations by 30% and 32%, respectively, has contributed to this trend in earlier recognition of ATTR-CM as well. However, despite increased disease awareness, earlier specific diagnosis, and therapeutic advances, ATTR-CM remains an important, under-recognised cause of heart failure leading to excess mortality, CV morbidity, impaired physical function, and QoL.

Anticipating novel therapies in development that could alter the course of ATTR-CM, in 2021 an expert panel recommended a set of criteria to monitor disease progression. The assessments fall into three domains:

- Clinical and functional domains: heart failure-related hospitalisations, New York Heart Association (NYHA) Classification, 6-Minute Walk Distance (6MWD), and Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Laboratory biomarkers domain: N-terminal prohormone of brain natriuretic peptide (NT-proBNP), troponin I (TnI), and National Amyloidosis Centre (NAC) ATTR-CM disease staging

Imaging (with imaging-based assessments of left ventricular [LV] structure or function) and ECG domains (conduction disturbances).

2.1.5. Management

Once the diagnosis of ATTR-CM is strongly suspected or has been newly established, it is recommended that the patient be promptly referred to a specialty amyloidosis clinic for further evaluation and confirmation of the diagnosis under the supervision of a cardiac amyloidosis specialist. A treatment plan should be established for both the cardiac and non cardiac manifestations of ATTR.

The cornerstone of the contemporary treatment of ATTR-CM centres on careful management of volume status with diuretics (mainly loop diuretics, but also potent tubular diuretics like metolazone). Aldosterone receptor antagonists may be useful as they are effective diuretics with a mechanism that is complementary to that of loop diuretics. The use of afterload reduction with renin-angiotensin antagonists (angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers, neutral endopeptidase inhibitors) and neurohormonal modulators (chronic, high dose beta blockade) are often poorly tolerated due to the restrictive physiology of infiltrative cardiomyopathy. Digoxin or calcium channel blockers are generally avoided in the management of ATTR-CM.

Patients with ATTR-CM are at high risk for the concomitant development of atrial fibrillation requiring both pharmacological and nonpharmacological interventions, as well as systemic anticoagulation for optimal clinical management.

Currently, tafamidis is the only targeted therapy approved for the treatment of ATTR-CM in the US and many other countries. The only other therapy in clinical use for the treatment of ATTR-CM is diflunisal, a nonselective COX inhibitor developed as a nonsteroidal anti-inflammatory drug that has TTR stabilizing activity. It is used off-label and sparingly in selected patients (given the risks of adverse reactions related to its COX inhibitory activity) and only where it is accessible, as it is not widely marketed.

Tafamidis is a small molecule that binds and stabilises the TTR tetramer. It was approved in the US for the treatment of ATTR-CM in 2019. Its registration for the treatment of ATTR CM was based primarily on the Phase 3 ATTR-ACT trial which enrolled 441 participants with ATTR CM in 2013 and 2014 and demonstrated a 30% and 32% relative risk reduction with tafamidis relative to placebo, on all-cause mortality and CV-related hospitalisation, respectively, after 30 months. Tafamidis also showed a lower rate of decline in 6MWD and Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS) versus placebo.

Despite this important therapeutic advance, a substantial medical need persists. In ATTR-ACT, about 30% of patients died in the combined active treatment arms, and the annualised rate of CV-related hospitalisation remained high at 0.48/year, with a benefit of tafamidis on CV-related hospitalisation emerging only after 9 months. In addition, the point estimate of CV-related hospitalisation was higher with tafamidis than placebo in the subgroup of patients with NYHA Class III. No clinically meaningful benefit was observed in the subgroup of participants with ATTR.

In a recently conducted, 12-month clinical study of the TTR knockdown agent patisiran, concomitant use of open-label tafamidis was frequent, and the incidence of progression on tafamidis was substantial, with 22% of patients who were on tafamidis alone (i.e., in the placebo arm relative to patisiran) showing worsening of heart failure by NYHA class after 12 months.

2.2. About the product

Acoramidis is an oral, high-affinity TTR stabiliser that acts to inhibit the dissociation of tetrameric TTR. It was rationally designed, informed by human genetics and structural biology, to mimic the stabilizing effects of T119M, a disease-protective gene variant, through a unique mode of binding to TTR. With respect to plasma protein binding, acoramidis has a higher free fraction, has higher binding affinity for both thyroxine binding sites, and employs a predominantly enthalpic binding mode involving hydrogen bonding, mimicking the T119M protective mutation's mechanism of enhanced stabilisation, as compared to other stabilisers (including but not limited to tafamidis).

2.3. Type of application and aspects on development

In the EU, orphan drug designation was granted on 19 November 2018 for the "treatment of ATTR amyloidosis" (EU/3/18/2081). The applicant requested the removal from the Community Register of Orphan Medicinal products on 5 December 2024.

The following Protocol Assistance was given by the CHMP:

- In March 2019 (EMEA/H/SA/4038/1/2019/PA/III), with questions related to the preclinical and clinical development of acoramidis.

- In April 2019 (EMEA/H/SA/4038/2/2019/PA/II), with questions related to the quality and preclinical development of acoramidis.
- In February 2021 (EMEA/H/SA/4031/FU/1/2020/PA/III), with questions related to the preclinical and clinical development of acoramidis.
- In February 2022 (EMA/HA/SA/0000082236), with questions related to the clinical development of acoramidis and revision to the statistical analysis of the primary endpoint.

On 23 August 2021, the applicant received confirmation of eligibility for the centralised procedure (CP) under Article 3(1) – Indent 4 – Orphan designated medicinal product of Regulation (EC) No 726/2004.

Due to delays in the clinical trial programme, the intent to submit the EU MAA was withdrawn in January 2022, which led to the cancelation of the CP eligibility request. Therefore, a new CP eligibility request was requested and subsequently granted on 26 April 2023 (product reference: H0006333).

The Anatomical Therapeutic Chemical (ATC) classification application for the active substance acoramidis was submitted in August 2023. In September 2023 the World Health Organization Collaborating Centre proposed the ATC code: C01EB25 acoramidis, with planned implementation in the ATC Index January 2025.

The main concern regarding the protocol assistance was concerning the advice from February 2022 (EMA/HA/SA/0000082236) where a change to the primary endpoint was proposed.

It is stated in the CHMP advice:

“Study AG10-301 has two primary endpoints. In order to control the overall type I error for the study at the 5% level, the Part A primary endpoint was initially assigned a two-sided alpha of 0.5% and the Part B primary endpoint a two-sided alpha of 4.5%. Thus, the study can formally be considered successful if at least one of the Part A and Part B primary endpoints are met.

In general, it is not acceptable to amend the primary endpoint of an ongoing clinical trial, especially if part of the study results are already known. The motivation for amending the definition of the Part B primary hierarchical composite endpoint to reduce the number of ties and hence increase the power of the study to detect a treatment effect is understood, but the proposed change is not supported.

The part A result on 6MWT was almost neutral (2m difference versus placebo) and it is likely that this informed what is in effect a downgrading of the 6MWT component in the Part B primary endpoint by including oral diuretic changes and NT-proBNP as additional events of clinical interest.

It is acknowledged that the COVID-19 pandemic may have impacted the trial considerably; however, the MAA will also include the post-COVID era. It is expected that at least part of the effect ascribed to COVID, such as the reduction in urgent care visits, is temporary. Using the COVID pandemic to weaken the primary endpoint is therefore not accepted. If the Applicant fears the number of ties in the Finkelstein-Schoenfeld procedure used for the primary analysis will be too high, they may consider to increase the follow-up time of the trial (e.g. by half the duration of the pandemic) or possibly include an objective criterion to define its new duration (e.g. mortality-percentage).

In any case, there are concerns as described in the following regarding the scientific validity of the amended endpoint as well as the suitability of the new endpoint components as measures of the patient’s well-being:

a) The proposal to expand the definition of treatment escalation events to include significant augmentation in oral diuretic therapy is not supported for the following reasons: In general, it is considered that the use of intravenous diuretic therapy is a better indicator of disease progression than an increase in the use of oral diuretics (Garcia-Pavia et al., 2021; doi: 10.1002/ejhf.2198).

Furthermore, it is not agreed that changes in oral diuretic therapy as listed by the Applicant are sufficiently justified to be defined as “significant augmentation” of this therapy. Firstly, the dose of furosemide was not taken into account. Secondly, the comparative efficacy data for different types of diuretic are limited. Although patients with resistance to oral furosemide therapy may benefit from trials with second-generation oral loop diuretics (bumetanide and torasemide), the evidence to recommend torasemide and bumetanide over furosemide in HF is limited (Buggey at al., 2016; doi: 10.1016/j.ahj.2014.12.009). No comparative studies addressing ethacrynic acid and furosemide appear to exist in the literature. Additionally, criteria for considering changes in oral diuretic therapy as treatment escalation were not pre-specified in the trial protocol. It is unclear if changes in oral diuretic therapy are being recorded in a systematic and consistent manner by trial investigators. As such, changes in oral diuretic therapy could be due to other reasons (safety, access, patient preference etc.) and not due to the need for treatment escalation.

b) The suggestion that difference in N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP) could be used as a surrogate endpoint for survival in patients with ATTR-CM and, hence, included as part of the morbidity component in the primary endpoint is not supported. Such surrogacy is not well-established. The proposed cut off point value (greater than 500 ng/L) is based on the results of a single study (Law et al., 2021; doi: 10.1136/heartjnl-2021-319063) which had significant methodological limitations, including a retrospective design and exclusion of patients who died within the first year of follow-up. Additionally, this study did not include patients receiving disease-modifying therapy and as such, was not designed to compare patients receiving treatment with those not treated. Furthermore, the use of biomarkers as primary endpoints in pivotal studies in patients with HF is not supported by the CHMP (see CPMP/EWP/235/95, Rev.2) and a mortality component is already included in the part B primary endpoint. Finally, NT-proBNP cannot be sensed by the patient is therefore not a relevant component of the primary endpoint.

c) CHMP has previously expressed concern with the introduction of the 6MWT as a component of the part B primary endpoint, while the trial was already fully enrolled. Moreover, the added information was considered limited given the fact that it is already assessed as part of the Part A primary endpoint.”

The applicant did not follow the above advice provided by the CHMP, where it was neither accepted to include 6-MWT nor NT-proBNP as additional components, and also the redefinition of diuretic use was not endorsed.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing acoramidis hydrochloride equivalent to 356 mg acoramidis as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E 460), croscarmellose sodium (E 468), colloidal hydrated silica (E 551), and magnesium stearate (E 470b)

Film-coat: macrogol poly(vinyl alcohol) grafted copolymer (E 1209), talc (E 553b), titanium dioxide (E 171), glyceryl monocaprylocaprate Type I (E 471), and poly(vinyl alcohol) (E 1203)

Printing ink: iron oxide black (E 172), propylene glycol (E 1520), and hypromellose 2910 (E 464)

The product is available in thermoformed dual-cavity blisters of PVC/PCTFE with aluminium foil lidding as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of the active substance is 3-[3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid hydrochloride (1:1) corresponding to the molecular formula $C_{15}H_{17}FN_2O_3$•HCl. It has a relative molecular weight of 328.77g/mol and the following structure:

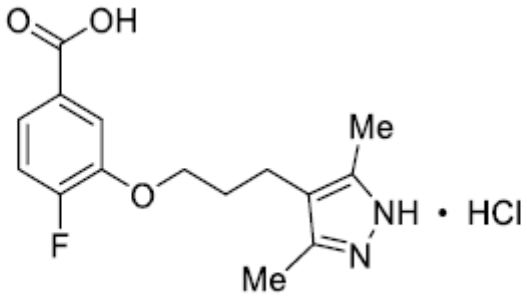


Figure 1: Active substance structure

The active substance is a slightly hygroscopic white to tan solid, highly soluble in aqueous media at either low pH (as the cation) or high pH (as the anion), but from pH 3.2 to 5.2, where acoramidis exists predominantly as the zwitterion, solubility is low.

The active substance does not exhibit stereoisomerism since the molecule is achiral.

Polymorphism has been observed for the active substance. The most stable form identified for is designated as Form A.

Manufacture, characterisation and process controls

The active substance is synthesised in 4 main steps followed by salt formation using well defined starting materials with acceptable specifications.

Several impurities were not listed as possible impurities in one of the starting materials. Therefore, the CHMP questioned the specification of this starting material as a major objection (MO). In response, the applicant justified the absence of these impurities, and the justification were considered satisfactory.

All compounds used in the active substance manufacturing process (starting materials, reagents, intermediates) and respective potential impurities (process related and degradation impurities) were evaluated according to ICH M7. The mutagenicity assessment identified some potentially mutagenic impurities. The control strategy for the potential mutagenic impurities has been provided including discussion of the carry over to final active substance and the control of impurities in the starting materials or intermediates. However, some additional mutagenic impurities potentially present in the process related to formation of were omitted from the initial discussion resulting in an MO. The applicant provided experimental demonstration that the relevant impurities are not present in the active substance at appreciable levels and can thus be omitted from the specification. This was considered acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, HPLC), polymorphic form (XRDP), assay (HPLC), impurities (HPLC), water content (KF), residual solvents (GC), residue on ignition (Ph. Eur.), and particle size (laser light diffraction).

The manufacturing process along with specifications for starting materials and intermediates ensures that the active substance consistently meets the required quality standards as defined in the active substance specification.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented. Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH), and under intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, water content, identification of polymorphic form, assay, organic impurities, and microbiological examination.

All results were within the proposed specifications.

Photostability testing following ICH guideline Q1B was performed on one batch. The active substance is photostable.

The active substance was exposed to ambient humidity at 20 and 50°C for 7 days. All quality attributes remained within the acceptance limits and no trends were observed. The active substance demonstrates excellent chemical and physical stability.

In addition, the active substance was exposed to forced degradation conditions (oxidation, basic conditions, acidic conditions, wet heat, dry heat, humidity and light irradiation) to evaluate susceptibility to chemical degradation. In solution, the active substance is stable under neutral and basic conditions, degradation was observed under extreme oxidation conditions. Also, slight degradation was detected after stress testing in solution under acidic conditions.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period of 48 months.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as white, oval, film-coated tablets, approximately 15 mm × 7.5 mm, with the BridgeBio company logo followed by “ACOR” in black ink on one side.

Pharmaceutical development efforts were focused on achieving adequate chemical stability, high drug load, and a rapid dissolution rate for the immediate release tablets.

The main physicochemical characteristics and biological properties of the active substance that can influence the development, manufacturability and performance of the finished products are properly provided.

Compatibility between active substance and excipients has been demonstrated in a stability programme.

The choice, function and quantities of excipients used in finished product are well explained and are based on wide use in the pharmaceutical market. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except the film-coating mixture and printing ink which are mixtures of common compendial excipients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The main goal of formulation development was to reduce the number of tablets patients would have to take per day. Formulations with different drug loads and different quantitative composition in excipients (same qualitative excipients) were selected for Phase 1 and 2 clinical trials. Further development focused on increasing the drug load and optimising the excipient content.

Further optimisation showed that a formulation with 66.7% active substance content was able to achieve a small tablet size for the 356 mg tablet which demonstrated comparable exposure to two 178 mg phase 1 tablets with 33% active substance content. This optimised formulation was used in phase 3 pivotal clinical trials remains unchanged except for the addition of printing ink which was added to the proposed commercial formulation which was used in primary stability studies.

An overview of the evolution of the dissolution method for the finished product was provided.

The chosen dissolution method was able to discriminate representative batches from batches manufactured with large active substance particle size and batches made with acoramidis free base. However, it is considered that a single acceptance criterion, derived following the decision tree for setting specifications based on the dissolution results of the biobatch as presented in EU Reflection Paper on dissolution (EMA/CHMP/CVMP/336031/2017) should be applied as the proposed specifications lead to rejection of “good batches” following storage under long term conditions. Therefore, the CHMP requested as an MO that the specification limit for the dissolution test of the finished product be revised. Supportive data showed that the three process validation batches would meet the revised specification. This was considered acceptable. A bioequivalence study was conducted comparing a single 356 mg tablet (66.7% API content) with two 178 mg tablets (33.3% API content) – the tablets were found to be similarly bioavailable.

The impact of the manufacturing process parameter variability on the finished product CQAs was evaluated, the manufacturing process is suitable for commercial scale and process validation.

The primary packaging is dual cavity PVC/PCTFE blisters with aluminium lidding foil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six steps: (1) mixing of the active substance with excipients; (2) blending; (3) tablet compression; (4) film coating; (5) printing of tablets; and (6) primary packaging.

Process validation data from three consecutive production scale batches of the finished product have been presented. All the process parameters, in-process and final product quality attributes successfully met the pre-determined specifications. The manufacture of the finished product is deemed validated at commercial scale.

The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), API polymorphic form (XRPD), dissolution (Ph. Eur.), water content (KF), uniformity of dosage units (Ph. Eur.), and microbial limits (Ph. Eur.).

During evaluation, the CHMP requested the applicant to investigate the dissociation of the active substance salt to HCl and the free base and discuss the potential impact on finished product quality as an MO. The applicant was requested to investigate the occurrence of this phenomenon in real and simulated worst case conditions during storage. The applicant demonstrated that the active substance dissociates over time by interaction with croscarmellose sodium to form acoramidis free base and sodium chloride. The applicant included a validated test for acoramidis free base in the finished product specification and the limit was tightened in line with the pivotal clinical batches at the request of CHMP. The MO was thus considered resolved.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Dimethylamine is a potential impurity in the active substance which could potentially react with adventitious nitrites in the finished product formulation to form NDMA. While the applicant considered this to be a low risk, the CHMP requested confirmatory testing using a suitably sensitive analytical method as an MO. The applicant tested active substance and finished product batches The applicant demonstrated that NDMA is not detected in the active substance or finished product. Therefore, no routine controls for nitrosamines are deemed necessary.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for pilot and commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 pilot scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH), for up to 24 months under intermediate conditions (30°C/75% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, assay, impurities, dissolution, and microbiological examination. The analytical procedures used are stability indicating.

No significant differences were observed under long term, intermediate and accelerated conditions for the primary and supportive batches.

One batch of the finished product was exposed to light as per ICH Q1B option 2. No significant differences were observed between the dark control and the light stressed sample. These data confirm that the finished product is photostable.

A stressed stability study was conducted on the finished product. Data demonstrate that the finished product is not impacted by freezing and is stable for the indicated duration at the temperatures tested.

Forced degradation studies were conducted as per ICH Q1A(R2) on the finished product. Under all tested conditions, no significant degradation was observed.

Based on available stability data, the proposed shelf-life as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure 5 MOs were raised related to potentially mutagenic impurities in a starting material, potentially mutagenic impurities in the active substance, of the initially proposed dissolution specification in the finished product, the impact of dissociation the active substance hydrochloride salt on finished product quality, and mitigation of the potential presence of NDMA in the finished product. The MOs were resolved by provision of additional data or further justification as follows: justification of omission of impurity limits in the starting material, provision of purge data to justify the omission of mutagenic impurity limits in the active substance, amendment of the dissolution method and tightening of the proposed limits, demonstration of dissociation of the active substance and inclusion of

a limit test for free base content, and provision of confirmatory testing data showing that NDMA is not detected in the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

ATTR is a systemic disease of protein instability. TTR is synthesised in the liver, pigmented retinal epithelium, and choroid plexus, with hepatocytes being the source of TTR in the systemic circulation. TTR, also called prealbumin, one of the transporters of the hormone thyroxine (T4) and retinol binding protein (RBP)-retinol (vitamin A) complex, form a complex under physiologic conditions. This complex is above the size limit for glomerular filtration and circulates with an approximate half-life of 2 to 3 days. The disease pathology of ATTR involves TTR tetramer dissociation into dimers which in turn lead to monomers, unfold and misassemble into oligomers and insoluble amyloid fibrils. The amyloid aggregates are deposited in a range of tissues, are cytotoxic and interfere with functional properties of the tissue; this leads to clinical manifestations of the disease. If left untreated, the disease is progressive and fatal regardless of which major clinical manifestation predominates (i.e., polyneuropathy or cardiomyopathy). ATTR is caused by extracellular accumulation of aggregates of either wild-type TTR (TTRwt) or TTRv amyloid protein.

Acoramidis (also known as AG10 and ALXN2060) is an oral, potent, highly selective, small molecule transthyretin (TTR) stabiliser under development for the treatment of transthyretin amyloidosis (ATTR) cardiomyopathy (ATTR-CM). Acoramidis stabilises TTR by mimicking the stabilising effects of T119M, the disease-protective TTR variant (TTRv) through its unique mode of binding to TTR.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies investigated the potency and selectivity of acoramidis, a TTR stabiliser, compared to tafamidis, another TTR stabiliser used in the treatment of ATTR-CM. Animal models were not used due to their inability to replicate the human phenotype of ATTR, particularly the deposition of fibrils in the heart. Thus, the characterisation of acoramidis utilised *in vitro* and pharmacodynamic (PD) measurements using purified TTR protein, in serum from widely used, non-genetically modified laboratory animals, and plasma samples from healthy donors and ATTRv-CM participants. The assays demonstrated that acoramidis binds to TTR with high affinity, occupying both T4 binding sites. In serum-based assays, acoramidis showed a dose-responsive effect, indicating TTR stabilisation. Additionally, the western blot assays revealed that acoramidis was more effective than tafamidis in stabilizing tetrameric TTR in plasma samples from participants with ATTR-CM, even at lower concentrations. *In vitro* metabolite profiling identified acoramidis-AG as the predominant metabolite in rats, dogs, monkeys, and humans. The affinity of acoramidis-AG to human TTR was found to be lower compared to acoramidis, with Kapp values of 241 nM and 1102 nM respectively in fluorescence polarisation assays. In Western blot assays, acoramidis-AG demonstrated only 24% to 34% of the activity of the parent compound acoramidis in stabilizing TTR in pooled human plasma. Differential pharmacokinetic parameters, such as potentially shorter half-life for the metabolite relative to acoramidis, may affect the actual contribution of acoramidis-AG to TTR stabilisation under physiologic conditions. Overall, the metabolite was found to be less pharmacologically active than its parent compound acoramidis.

The *in vivo* pharmacodynamics of acoramidis were assessed by correlating its circulating levels in serum samples from dogs and monkeys with its ability to stabilise TTR. A circulating concentration of around 10 µM was found to be sufficient for near-complete TTR stabilisation. Regarding the impact on

thyroid function, modest reductions in serum free T4 levels were observed with acoramidis treatment, consistent with findings from tafamidis. These changes were not associated with clinical thyroid dysfunction, suggesting no safety concerns related to this effect. Furthermore, acoramidis treatment led to reductions in serum retinol binding protein (RBP) levels, likely due to its primary role as a carrier protein for holo-RBP. These reductions were not deemed concerning for safety and were consistent with observations from tafamidis treatment, where reductions in RBP levels were not correlated with clinical issues related to retinol transport or vision problems. These findings suggest that acoramidis has the potential to be an effective treatment for patients with ATTRv, regardless of variant genotype, by stabilizing TTR and potentially improving clinical outcomes.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacology tests showed a lack of cytotoxic or antiproliferative effect of acoramidis on four mammalian cell lines (Hep3B, Jurkat, MCF3, Hela) (UOP 2020-005). Off-target activity was not detected when acoramidis at a concentration of 100 µM was tested in Panlabs (Eurofin) panel of receptors, enzymes and ion channels. In contrast to known TTR ligands and cyclooxygenase (COX) inhibitors such as diflunisal, acoramidis does not inhibit COX enzymes or bind to thyroid hormone nuclear receptor at the tested concentration, thus no off-target activity is anticipated against these proteins.

2.5.2.3. Safety pharmacology programme

Safety pharmacology was evaluated in GLP rat respiratory and central nervous system (CNS) safety studies conducted with a single dose of up to 1000 mg/kg. Acoramidis was also assessed *in vitro* and *in vivo* for cardiovascular safety. GLP hERG patch clamp assay did not reach half maximal response in hERG current inhibition (3.2% inhibition at 10 µM and 2.1% inhibition at 50 µM). The reported IC50 of >50 µM represents a >33-fold margin over the free fraction of the high clinical exposure estimated at 12,300 ng/mL. A GLP dog telemetry study demonstrated no concentration QT effect at multiple plasma concentrations above the high clinical exposure estimated at 12,300 ng/mL, the upper bound of the 95% CI for the day 28, 1 hour postdose concentrations observed in the PK/PD sub-study of AG10-301 (48.2 fold margin). Based on *in vitro* metabolite profiling by hepatocyte incubation, acoramidis-β-D-glucuronide (acoramidis acylglucuronide [acoramidis-AG]) was identified as the predominant metabolite. Acoramidis-AG was also detected as a metabolite in plasma samples of rats, dogs and monkeys dosed with acoramidis. However, the low circulating plasma exposure of the metabolite (7.64% of the total radioactivity AUC based on the 14C human ADME study) limits the potential contribution of acoramidis-AG to safety pharmacology issues.

2.5.2.4. Pharmacodynamic drug interactions

Treatment with acoramidis leads to a modest decrease in serum free T4 levels, resulting from the interaction between acoramidis and the natural ligand T4 at the binding sites on tetrameric TTR. However, these changes are not considered clinically significant or concerning for safety.

2.5.3. Pharmacokinetics

An extensive nonclinical programme investigating PK and ADME has been carried out for acoramidis in nonclinical species and *in vitro*. The PK of acoramidis and its metabolite acoramidis-AG were characterised in the chronic rat and dog toxicology studies based on *in vitro* and nonclinical *in vivo* metabolism data.

Liquid chromatography with tandem mass spectrometry (LC MS/MS) was employed in PK and TK studies for measuring plasma concentrations of acoramidis and acoramidis-AG. Assays were developed and validated for toxicology studies in rats, dogs, and rabbits, following FDA and EMA guidance. Radioactivity levels in various samples were determined using liquid scintillation counting and quantitative whole-body autoradiography (QWBA). Metabolite concentrations and profiles were analysed using high-performance liquid chromatography with radiochemical detection, with further elucidation of metabolite structures conducted using LC-MS/MS.

Following IV administration, systemic clearance of acoramidis in mice, rats, dogs, and monkeys was low, as was the Vss. Terminal t1/2 was relatively long, ranging from 5.32 to 19.4 hours. Following oral administration, Cmax was reached rapidly, with Tmax values ranging from 0.500 to 2.67 hours across species. Acoramidis was well absorbed and absolute oral bioavailability values ranged from 30.5% to 59.7% in the 4 species. Following repeated doses of acoramidis to rats, dogs, and CbyB6F1-Tg[HRAS]2Jic wild-type mice, in general, no sex differences (<2-fold) were observed in acoramidis plasma exposures, and the plasma exposure of acoramidis increased generally dose proportionally with increasing dose, with a few exceptions. No accumulation was observed after a short-term duration of multiple doses; however, a modest accumulation was observed after longer duration multiple dosing in both rats and dogs.

Acoramidis is highly protein bound, with plasma protein binding ranging from 87% to 99% across species. There were no marked species differences or concentration-dependent blood partitioning, and acoramidis does not distribute into the brain. Tissue distribution of [14C]acoramidis derived radioactivity in pigmented Long Evans male rats after oral administration was extensive, and the highest Cmax levels were observed in liver, arterial walls, adrenal glands, kidneys (including renal cortex), and stomach. Tissues with the lowest Cmax values were observed for non-circumventricular central nervous system tissues, abdominal fat, seminal vesicles, nasal turbinates, and testes. The medulla oblongata and olfactory lobe were devoid of radioactivity throughout the time course of this study. Overall, there was no accumulation or retention of radioactivity in tissues. The data also suggested that [14C]acoramidis derived radioactivity did not selectively associate with melanin containing tissues in the pigmented rat.

Following a single oral dose of [14C]acoramidis in rats and dogs, glucuronidation was the predominant biotransformation pathway, whereas oxidation and glycine conjugation were comparatively minor metabolic pathways for acoramidis. This is consistent with what was observed *in vitro* in mouse, rat, dog, monkey, and human hepatocytes. Acoramidis was the major component in plasma, urine, and faeces in both rats and dogs. Its direct acylglucuronide conjugate and, to a lesser extent, its acylglucuronide isomers were the most abundant metabolites in plasma and bile in rats, and the most abundant circulating and, albeit minor, urinary metabolite in dogs. Exposures of the metabolite, acoramidis-AG, were measured in the chronic 26-week rat and 39-week dog toxicology studies to ensure that the metabolite was not formed at disproportionately higher levels in humans compared to either to the species used in the toxicology studies. The results indicate that the exposure of the metabolite achieved in the toxicology species was sufficient to cover that observed in humans.

The elimination of [14C]acoramidis derived radioactivity in rats and dogs occurred predominantly by faecal excretion. Mean faecal excretion accounted for 79.0% and 71.7% of the dose for intact male and female rats, respectively, whereas mean urinary excretion accounted for 16.3% and 24.8% of the dose for intact male and female rats, respectively. Mean faecal excretion accounted for 51.0% and 66.0% of the dose for male and female dogs, respectively, whereas mean urinary excretion accounted for 34.4% and 27.8% of the dose for male and female dogs, respectively. The excretion data obtained from BDC male rats indicated that biliary excretion was involved in the elimination of [14C]acoramidis derived radioactivity.

There is minimal cytochrome P450 involvement in the metabolism of acoramidis. Acoramidis did not significantly inhibit any of the 7 major human CYP450 isoforms when tested in HLM (Reported IC_{50} > 150 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9, and CYP2D6; Reported IC_{50} > 1100 µM for CYP3A4/5). From preclinical studies, an irreversible inhibition of CYP2C8 and CYP2C9 is reported (IC50 values of 76 µM and 100 µM, respectively). As CYP2C8 and CYP2C9 are responsible for the metabolism of a very large number of drugs with a narrow therapeutic index, and given that a dedicated DDI clinical study was not performed, the following sentence was included in the SmPC section 4.5: "*Based on in vitro studies, acoramidis is unlikely to cause any clinically relevant uridine 5'-diphospho (UDP)-glucuronosyl transferase-dependent or Cytochrome P450 dependent interactions. However, acoramidis was shown to be a weak inhibitor of CYP2C8 and CYP2C9 in vitro. No in vivo study has been performed. Therefore, concomitant CYP2C8 and CYP2C9 substrates with narrow therapeutic index should be used with caution".*

There was little to no induction of CYP1A2, CYP2B6 and CYP3A4 as measured by mRNA expression (< 2-fold change) following treatment with up to 150 µM acoramidis with a few exceptions. These data suggest that acoramidis is unlikely to cause any clinically relevant CYP-dependent DDIs.

Acoramidis-AG formation is mainly catalysed by UGT1A9 *in vitro*, with UGT1A1 and UGT2B7 potentially playing a minor role. Acoramidis was a direct inhibitor of UGT1A9 using HLM (IC50 = 150 µM) and rUGT1A9 (IC50 = 40 µM). There was minimal direct inhibition of UGT1A1 and UGT2B7 (IC50 > 200 µM using HLM and IC50 > 150 µM using rUGT1A1 and rUGT2B7). These data suggest that acoramidis is unlikely to cause any clinically relevant UGT-dependent DDIs.

Acoramidis is not a substrate for OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, or BSEP, but is a substrate for OAT1 and BCRP *in vitro*. However, for OAT1, the Km value was determined to be 28.5 µM with a Vmax of 45.4 pmol/min/cm2, and for BCRP, the Km value is > 100 µM, and the Vmax value could not be determined. Given the high Km values and the relatively low amounts of intact acoramidis excreted in urine, no clinically significant DDIs are anticipated for acoramidis as substrate of these transporters.

No significant inhibition of transport mediated by human OCT1, OCT2, OATP1B1, OATP1B3, MATE2-K, BSEP, BCRP, or P-gp was observed in vitro. However, acoramidis inhibits transport mediated by OAT1, OAT3, and MATE-1 *in vitro*, with IC50 values estimated to be 1.39 µM, 1.26 µM, and 178 µM respectively. Based on the calculated Imax,u/IC50 values, there may be potential for clinical DDIs with OAT1/OAT3 substrates like loop diuretics (e.g., furosemide) which are the most common co-medication class used to manage heart failure in ATTR-CM patients. This potential for clinical DDIs with OAT1 and OAT3 substrates has been assessed by PBPK modelling and by a clinical DDI study and is referred to in the SmPC.

Since no clinically significant DDIs are anticipated for acoramidis as a victim, the Sponsor does not anticipate resulting increased exposures of acoramidis-AG. The clinical exposure of the metabolite has been covered in the non-clinical species with safety ratios ≥ 12. Furthermore, the stability of acoramidis-AG in phosphate buffer has been evaluated as a surrogate indicator of its reactivity. Based on the longer half-life (161 min), acoramidis-AG as a low potential for covalent binding. Acoramidis-AG has also been shown to have only 24% to 34% activity of that of parent acoramidis by a western blot TTR stabilisation assay. TRA/LC-MS/MS data from the human ADME study (AG10-007) has shown that approximately 7.64% of the circulating TRA is associated with plasma acoramidis-AG AUC. Based on these data, the Sponsor does not anticipate any clinically significant issues arising from a DDI perspective of acoramidis-AG.

In general, the systemic exposure and metabolism defined in the species used for toxicological assessment indicates that the species used were appropriate for the safety of acoramidis and its metabolites in humans. The results of *in vitro* and *in vivo* non-clinical PK, TK, drug metabolism, and

DDI studies provide a good characterisation of the pre-clinical drug metabolism and PK profile of acoramidis.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies have been conducted.

The lack of single dose toxicity studies is considered acceptable taking into account current guidelines and data from short-term toxicity studies.

2.5.4.2. Repeat dose toxicity

Repeated dose toxicity studies comprised studies in rats and dogs with once daily administration of acoramidis by oral gavage during up to 26 and 39 weeks, respectively. Except for 3 studies with a treatment duration of 7 days, all the others were GLP compliant. All studies included toxicokinetic analysis for acoramidis. Additionally, chronic toxicity studies have also included toxicokinetic analysis for the metabolite acoramidis-acylglucuronide.

In general, toxicokinetic data for acoramidis showed no significant accumulation after multiple doses or sex differences in exposure. Exposure, as assessed by acoramidis Cmax and AUC values, increased with the increase in dose level.

The three 7-day non-pivotal studies comprised one study in rats and two studies in dogs. The maximum tested dose in the study in rats was 1000 mg/kg/day; in the studies in dogs were 200 mg/kg/day, in the first study, and 1000 mg/kg/day, in the second. Adverse effects were observed in the second study in dogs only. These consisted of gastrointestinal effects (vomits and liquid/nonformed faeces) observed at ≥ 200 mg/kg/day, corresponding to a mean systemic exposure (AUC0-24) 12-fold that expected in patients. The MTD in this study was determined at 600 mg/kg/day, corresponding to a mean systemic exposure 82-fold that expected in patients. Systemic exposures to acoramidis attained in the other two 7-day studies were up to 77-fold (rat) and 9-fold (dog) those expected in patients.

The pivotal repeated dose toxicity studies comprised studies of 4, 13 and 26 weeks in rats, and of 4, 13 and 39 weeks in dogs. Tested dose levels in studies in rats were 50, 200, 600 and 1000 mg/kg/day, in the 4-week study; 50, 350 and 1000 mg/kg/day, in the 13-week study; and 50, 300 and 600 mg/kg/day, in the 26-week study. Tested dose levels in studies in dogs were 50, 200, 400 and 600 mg/kg/day, in 4-week study; 50, 125 and 300 mg/kg/day, in the 13-week study; and 50, 112 and 250 mg/kg/day, in the 39-week study.

Effects considered to be adverse were observed in two studies only, the 13-week study in rats and the 4-week study in dogs. In the 13-week study in rats, adverse decrease in body weight and mortality were observed at the maximum tested dose. In the 4-week study in dogs, vomits and liquid/nonformed faeces were observed at the maximum tested dose. Additionally, at ≥ 400 mg/kg/day, there were histological changes in the heart - slight or moderate myocardial degeneration/necrosis and slight or moderate mononuclear cell infiltrates at ≥ 400 mg/kg/day and also light haemorrhage and/or moderate fibrosis at 600 mg/kg/day. The NOAELs for the 13-week study in rats and the 4-week study in dogs were set at 350 and 200 mg/kg/day, respectively.

For the two studies with observed adverse effects, systemic exposures (AUC0-24) at the NOAEL were 21-fold and 7-fold the expected human exposure in rats and dogs, respectively. Furthermore, cardiac histological findings in the 4-week study in dogs were considered incidental. They were not detected in

the longer-term studies in the same species, no changes in cardiac troponin were observed in the chronic toxicity study and similar incidental findings have been reported in published studies.

Systemic exposures attained in the remaining studies were up to 51- and 33-fold human exposure in the 4- and 26-week studies in rats, respectively; and 12- and 25-fold human exposure in the 13- and 39-week studies in dogs, respectively.

Regarding systemic exposure to the metabolite acoramidis-acylglucuronide, in the chronic toxicity studies, exposure (AUC0-last) to this metabolite at the NOAEL (and also maximum tested doses) were 16- and 26-fold human exposure in rats and dogs, respectively.

It is, therefore, concluded that results from the repeated dose toxicity studies do not suggest a risk of toxicity for patients at the intended therapeutic dose level. The package of repeated dose toxicity studies is adequate, and no particular issues have been identified related, for instance, with relevance of animal species, GLP, or negative control contaminations.

2.5.4.3. Genotoxicity

The genotoxic potential of acoramidis was assessed in a battery of three genotoxicity studies and includes an *in vitro* Ames test (8358481) and two *in vivo* studies: micronucleus and comet assays (8358482). All studies were negative for genotoxic findings suggesting that acoramidis is not mutagenic and there is a low genotoxic potential to cause injury to humans.

2.5.4.4. Carcinogenicity

The carcinogenicity programme included a pre-carcinogenicity study in mice, 26-week carcinogenicity study in transgenic mice, and 104-week carcinogenicity in rats.

A pivotal GLP study was designed to determine the carcinogenic potential of acoramidis, when administered daily by oral gavage to 001178-T (hemizygous) rasH2 mice for at least 26 weeks. Daily oral administration of vehicle control article or 30, 100, or 300 mg/kg/day acoramidis to male or female 001178-T (hemizygous) rasH2 mice for 26 weeks had no impact on survival or mortality, clinical observations, body weight, or food consumption. No acoramidis-related neoplasms, organ weight effects, macroscopic findings, or microscopic findings were observed. Therefore, no carcinogenic potential was observed for acoramidis.

Another pivotal GLP study evaluated the carcinogenic potential and to determine the TK of acoramidis, when administered daily by oral gavage to Hsd:Sprague Dawley rats for at least 104 weeks. The administrations of 5, 15, or 50 mg/kg/day acoramidis (males) or 40, 120, or 350 mg/kg/day (females) via oral gavage were clinically tolerated, and no effects on survival were noted. No acoramidis dose level provided clear evidence of carcinogenic potential in either sex, although acoramidis-related increased incidence of proliferative, non-neoplastic microscopic findings was noted in the adrenal cortex and pancreas of males. In the adrenal cortex, increased incidence and/or severity of zona fasciculata hyperplasia were noted for males administered ≥ 15 mg/kg/day, and in the pancreas, an increased incidence of islet cell hyperplasia was noted for males administered 15 mg/kg/day. Based on these findings, the neoplastic NOAEL for acoramidis is 50 mg/kg/day for males and 350 mg/kg/day for females. For males, this dose level corresponded to mean C_{max} and AUC_{last} values of 49.1 µg/mL and 126 µg*hr/mL, respectively, on day 176. For females, this dose level corresponded to mean C_{max} and AUC_{last} values of 218 µg/mL and 1250 µg*hr/mL, respectively, on day 176.

Acoramidis was negative for genotoxic findings suggesting there is a low risk of genotoxic injury to human subjects and considering that acoramidis did not show any carcinogenic potential when evaluated in 26-week carcinogenicity study in transgenic mice, and 104-week carcinogenicity study in rats. In general, considering the weight of evidence including repeated-dose toxicity study results and mode of action, it may be concluded that the carcinogenicity potential is very low or inexistent.

2.5.4.5. Reproductive and developmental toxicity

Developmental and reproductive toxicology studies comprised studies on male and female fertility and early embryonic development, in rats, embryo-foetal development, in rats and rabbits, and pre- and post-natal development, in rats. In all studies, acoramidis was administered once daily by oral gavage. Except for dose range finding embryo-foetal development studies, all the others were GLP compliant.

Fertility and early embryonic development:

In the male and female fertility and early embryonic development study, acoramidis was administered at dose levels of 50, 350 or 1000 mg/kg/day.

The study revealed general toxicity in both males and females. Additionally, at 1000 mg/kg/day, there were statistically significant fewer mean number of oestrous cycles and 9 females exhibited persistent dioestrus. The findings, although considered test article-related, were stated to be within the Testing Facility Historical Control Data range. No adverse effects were identified regarding the F1 generation.

Based on reductions in body weight gains, the NOAEL for general toxicity in males and females were set at 50 and 350 mg/kg/day, respectively. The NOAEL for reproductive toxicity and the F1 generation were both set at 1000 mg/kg/day.

The study has not included a toxicokinetic analysis. Based on data from the repeated dose toxicity studies in rats, it is estimated that systemic exposure (AUC) in rats at 1000 mg/kg/day was 50-fold human exposure.

Embryo-foetal development:

Embryo-foetal development studies comprised pivotal studies in rats and rabbis and the respective preceding dose range finding studies, all with acoramidis administered once a day by oral gavage.

Tested doses levels in the non-pivotal studies were 50, 350 and 1000 mg/kg/day, in rats, and 50, 350 and 1000 mg/kg/day, in rabbits. In the pivotal studies, these were 50, 350 and 1000 mg/kg/day, in rats, and 25, 75 and 200 mg/kg/day, in rabbits. Both pivotal studies included toxicokinetic data for both acoramidis and the metabolite acoramidis-acylglucuronide.

No adverse effects were observed in the pivotal studies. In both species, the NOAEL for maternal toxicity and embryo-foetal development was set at the maximum tested doses, i.e., 1000 mg/kg/day in rats and 200 mg/kg/day in rabbits. These correspond to systemic exposures (AUC) to acoramidis 39- and 15-fold higher than human exposure in rats and rabbits, respectively.

No teratogenicity or embryo-foetal lethality were observed in the non-pivotal studies.

Prenatal and postnatal development:

Pre- and post-natal development studies comprised a study in rats. In this study, acoramidis was administered from GD 6 through LD 20 at the tested dose levels of 50, 350 and 1000 mg/kg/day.

Maternal toxicity, with statistically significant lower mean body weight and food consumption values, and a decrease in viable foetuses, due to resorption, were observed at 1000 mg/kg/day. Additionally, animals from the F1 generation showed adverse decrease in body weight, at 1000 mg/kg/day, and

learning deficits (proximal and spatial learning) at ≥350 mg/kg/day which were considered adverse at 1000 mg/kg/day.

No acoramidis-related F1 mortality or clinical observations, or effects on pup developmental landmarks, food consumption, gestational body weights, oestrous evaluation, reproductive indices, caesarean section parameters, or macroscopic observations were noted for any dose level. The NOAEL for both maternal toxicity and the F_1 generation was set at 350 mg/kg/day.

The study has not included a toxicokinetic analysis. Based on data from the repeated dose toxicity studies in rats, it is estimated that systemic exposure (AUC) in rats at 350 mg/kg/day was 21-fold human exposure.

Juvenile animal studies:

Juvenile animal studies have not been conducted.

The package of developmental and reproductive toxicology studies is considered adequate. The lack of juvenile animal studies is acceptable. The medicinal product has been granted a product-specific waiver for all subsets of the paediatric population.

2.5.4.6. Toxicokinetic data

Toxicokinetic analysis has been included in various study types, namely, repeated dose toxicity, embryo-foetal development and carcinogenicity. Data for these different studies is already addressed in their respective sections. In general, toxicokinetic data for acoramidis showed no significant accumulation after multiple doses or sex differences in exposure. Exposure, as assessed by acoramidis C_{max} and AUC values, increased with the increase in dose level.

2.5.4.7. Local tolerance

No dedicated local tolerance studies were conducted as medicinal products intended for oral administration do not require such a study.

2.5.4.8. Other toxicity studies

In an *in vitro* phototoxicity assay in mouse fibroblasts, acoramidis demonstrated a low potential for phototoxicity and unlikely to be a safety concern for humans. In silico analysis of acoramidis impurities suggested an unlikely potential for genotoxicity.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment (ERA) for acoramidis following the *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SWP/4447/00 corr.2, 2006) and the Questions and answers on *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016).

Relevant endpoints, methods used and results obtained were discussed and summarised in Table 1.

Table 1: Summary of main study results

Substance (INN/Invented Name): Acoramidis HCl
CAS-number (if available):

PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	2.51 ± 0.01 (pH=4) 2.39 ± 0.04 (pH=5 0.52 ± 0.07 (pH=7) -0.69 ± 0.01 (pH=9)			Potential PBT: N
PBT-assessment					
Parameter	Result relevant for conclusion				Conclusion
Bioaccumulation	log K_{ow}	< 3 (pH 7.0)			Not B
	BCF	Log Kow < 3			Not B
Persistence	DT50 Values are derived from the OECD 308 study below and have been recalculated to 12°C	$DT_{50\ total\ system}$ =311.6 d, 727.7 d			vP
Toxicity	NOEC	8.09 mg/L (free base)not			not T
PBT-statement :	Acoramidis HCl is not considered as PBT nor vPvB				
Phase I					
Calculation	Value			Unit	Conclusion
PEC_{sw}, default	0.21			µg/L	≥ 0.01 threshold: Y Phase environmental fate and effects analysis are needed.
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption Soil 1 = sandy silt loam Soil 2 = loamy sand Soil 3 = clay Sludge 1 = Loughborough Sludge 2 = Worlingworth	OECD 106	$K_{oc,\ soil\ 1}$ = 185 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 431 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 37.1 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 51.8 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 50.1 L/kg_{oc}			Do not trigger further studies as Koc for the two sludges and 3 soils < the trigger value of 1000 L/kg
Ready Biodegradability Test	OECD 301B	0% biodegradation (28 days)			Not readily biodegradable
Aerobic and Anaerobic Transformation in two Aquatic Sediment Systems Sediment 1 = Calwich Abbey Lake System (CAL) (silt loam) Sediment 2 = Lumsdale Middle Pond System (LMP) (sand)	OECD 308	$DT_{50,\ water}$ = 30.7 d (1), 37.3 d (2) $DT_{50,\ sediment}$ = not calculable $DT_{50,\ total\ system}$ = 146 d (1), 341 d (2) % shifting to sediment = 37.0 % (1), 50.4 % (2) Volatiles: 2.9% (1); 0.5% (2P) NER = 23.3 % (1);30.4% (2) Transformation products >10% = No			DT50s at 20°C At day 14 (%parent + %NER) >10% acoramidis has shifted to the sediment. Need for further investigation of effects on sediment-dwelling organisms Chironomus *riparius* at test end
Phase IIa Effect studies					
Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test *(Raphidocelis subcapitata)*	OECD 201	NOEC	2.76 x10^4	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	8.1 x10^3	µg/L	All end endpoints
Fish, Early Life Stage Toxicity Test (*Pimephales promelas*)	OECD 210	NOEC	8.89 x10^3	µg/L	All end endpoints

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	2.84 x10^5	µg/L	Respiration
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius)*	OECD 218	NOEC	3865	mg/kg_{dw}	Corrected for 10% organic carbon

Phase I

Based on European prevalence data of transthyretin amyloidosis in adult patients with cardiomyopathy, published in 2022, the refined Fpen for PEC surface water was calculated. Sweden was selected as the worst case (with the highest disease prevalence), resulting in the refined Fpen value of 0.00005. The PECsw refined value calculated for acoramidis exceeds the established limit in the guideline (0.01 µg/L), a Phase II environmental fate and effects analysis was performed by the applicant.

The shake flask method (OECD Guideline107) was used to determine the octanol-water partition coefficient values of acoramidis HCl at all environmentally relevant pHs. At pH 4, pH 5, pH 7, and pH 9 log Dow values of 2.51, 2.39, 0.52 and -0.69 were found respectively. As these values are below the action limit of 4.5, no further assessment for persistence, bioaccumulation and toxicity should be performed.

As the Koc in sewage sludge was <10,000 L/Kg acoramidis is unlikely to reach the soil compartment, and a Phase II Tier A exposure and effect assessment for soil was not triggered.

As acoramidis HCl was not readily biodegradable, it is considered a potentially persistent substance. To assess persistence an OECD 308 study was performed. Since > 10% of acoramidis shifted from the water phase to the sediment 14 days after application further investigation of effects on sediment-dwelling organisms was conducted. Low risk (RQ < 1 was calculated for sediment-dwelling organisms further testing in sediment is required. "Acoramidis is not expected to present a risk to the soil environment."

The presented risk ratios (PEC/PNEC) for various environmental compartments (such as surface water, groundwater, and soil) are well below the action limits, indicating no environmental risk.

Acoramidis is unlikely to pose a risk to the aquatic, sediment and soil environments.

2.5.6. Discussion on non-clinical aspects

The data submitted for assessment is generally in accordance with the legal requirements and available guidelines.

The *in vitro* and *in vivo/ex vivo* studies in multiple species, including human subjects with ATTR-CM wild type and variant, have described the targeted pharmacology of acoramidis. Biochemical studies have established interspecies sensitivity and have measured selectivity of acoramidis for TTR from various species. The measured pharmacologic effects of acoramidis are dose-dependent in dogs and monkeys and can be monitored with a PK/PD relationship across a broad range of exposures. Safety pharmacology studies in rats and dogs established a low risk of interference at target therapeutic levels of acoramidis. The results provide support for acoramidis' mechanism of binding to TTR, ability to stabilise the tetrameric form of both TTRwt and TTRv in serum and plasma and establishes appropriate target therapeutic exposures in human subjects.

In general, the systemic exposure and metabolism defined in the species used for toxicological assessment indicates that the species used were appropriate for the safety of acoramidis and its metabolites in humans. The results of *in vitro* and *in vivo* non-clinical PK, TK, drug metabolism, and

DDI studies provide a good characterisation of the pre-clinical drug metabolism and PK profile of acoramidis.

There is minimal cytochrome P450 involvement in the metabolism of acoramidis. Acoramidis did not significantly inhibit any of the 7 major human CYP450 isoforms when tested in HLM (Reported IC_{50} > 150 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9, and CYP2D6; Reported IC_{50} > 1100 µM for CYP3A4/5). From preclinical studies, an irreversible inhibition of CYP2C8 and CYP2C9 is reported (IC50 values of 76 µM and 100 µM, respectively). As CYP2C8 and CYP2C9 are responsible for the metabolism of a very large number of drugs with a narrow therapeutic index and, given that a dedicated DDI clinical study was not performed, the following sentence was included in the SmPC section 4.5:" *Based on in vitro studies, acoramidis is unlikely to cause any clinically relevant uridine 5'-diphospho (UDP)-glucuronosyl transferase-dependent or Cytochrome P450-dependent interactions. However, acoramidis was shown to be a weak inhibitor of CYP2C8 and CYP2C9 in vitro. No in vivo study has been performed. Therefore, concomitant CYP2C8 and CYP2C9 substrates with narrow therapeutic index should be used with caution".*

The lack of single dose toxicity studies is considered acceptable considering current guidelines and data from short-term toxicity studies. In general, toxicokinetic data for acoramidis showed no significant accumulation after multiple doses or sex differences in exposure. Exposure, as assessed by acoramidis C_{max} and AUC values, increased with the increase in dose level.

Effects considered to be adverse were observed in two studies only, the 13-week study in rats and the 4-week study in dogs. In the 13-week study in rats, adverse decrease in body weight and mortality were observed at the maximum tested dose. In the 4-week study in dogs, vomits and liquid/nonformed faeces were observed at the maximum tested dose. Additionally, at ≥ 400 mg/kg/day, there were histological changes in the heart - slight or moderate myocardial degeneration/necrosis and slight or moderate mononuclear cell infiltrates at ≥ 400 mg/kg/day and also light haemorrhage and/or moderate fibrosis at 600 mg/kg/day. The NOAELs for the 13-week study in rats and the 4-week study in dogs were set at 350 and 200 mg/kg/day, respectively.

For the two studies with observed adverse effects, systemic exposures (AUC_{0-24}) at the NOAEL were 21- and 7-fold the expected human exposure, in rats and dogs, respectively. Furthermore, cardiac histological findings in the 4-week study in dogs were considered incidental.

Systemic exposures attained in the remaining studies were up to 51- and 33-fold human exposure in the 4- and 26-week studies in rats, respectively; and 12- and 25-fold human exposure in the 13- and 39-week studies in dogs, respectively. Regarding systemic exposure to the metabolite acoramidis-acylglucuronide, in the chronic toxicity studies, exposure (AUC_{0-last}) to this metabolite at the NOAEL (and also maximum tested doses) were 16- and 26-fold human exposure in rats and dogs, respectively.

Results from the repeated dose toxicity studies do not suggest a risk of toxicity for patients at the intended therapeutic dose level.

The package of repeated dose toxicity studies is adequate, and no issues have been identified related, for instance, with relevance of animal species, GLP, or negative control contaminations.

All studies for the genotoxicity potential were negative suggesting that acoramidis is not mutagenic and there is a low genotoxic potential to cause injury to humans.

Acoramidis did not show any carcinogenic potential when evaluated in 26-week carcinogenicity study in transgenic mice, and 104-week carcinogenicity study in rats. Considering the weight of evidence including repeated-dose toxicity study results and mode of action, it may be concluded that the carcinogenicity potential is very low or inexistent.

Acoramidis was evaluated in a complete nonclinical developmental and reproductive toxicity programme in line with ICH Guideline (ICH S5 [R3], 2020). Developmental and reproductive toxicology studies comprised studies on male and female fertility and early embryonic development, in rats, embryo-fetal development, in rats and rabbits, and pre- and post-natal development, in rats. In all studies, acoramidis was administered once daily by oral gavage. Except for dose range finding embryo-foetal development studies, all the others were GLP compliant.

The package of developmental and reproductive toxicology studies is considered adequate. The lack of juvenile animal studies is acceptable. The medicinal product has been granted a product-specific waiver for all subsets of the paediatric population.

Results from the conducted studies on male and female fertility and early embryonic development do not indicate a risk of adverse effects. The NOAEL for reproductive toxicity was set at 1000 mg/kg/day, the maximum tested dose. At this dose level significant lower numbers of oestrous stages in the 14-day premating period and persistent dioestrus were observed in females. Although these findings were significant and treatment-related they were not considered adverse as they lay within the historical control data range of the testing facility and had no impact on mating and fertility. No toxicokinetics of acoramidis and the acylgluroronide have been investigated in this study. Based on exposure data from repeat-dose toxicity studies in rats the AUC-derived acoramidis-exposure margin to human exposure at the MRHD is around 50-fold based on AUC-levels.

In the embryo-foetal development toxicity studies with acoramidis in rats and rabbits, no acoramidis-related effects considered to be adverse were observed on embryo-foetal development and viability. In both studies the NOAEL for maternal toxicity and embryo-foetal development is proposed to be at the highest dose level of 1000 mg/kg/day and 200 mg/kg/day for rats and rabbits, respectively. AUC-based exposure margins at the highest dose group in studies to human exposure at the MRHD is 39-fold for rats and 15-fold for rabbits.

In the embryo-foetal development toxicity study in rats, an increase in post-implantation loss was observed in the 1000 mg/kg/day dose group compared to the control and lower dose groups (0.6/0.4/0.5/2.4) which included 2 litters with 100% resorption. However, the incidence of post-implantation loss was within historical control data and the increase was not statistically significant.

Reproductive toxicity has been observed in the pre- and post-natal development study with a decrease in viable foetuses, lower F_1 body weights – which persisted after weaning but recovered to comparable amount of weight to controls starting approximately 2 weeks into the maturation phase - and learning deficits.

In the water-maze test performed on PND 63 acoramidis-related effects on proximal and spatial learning deficits were noted for pups from animals administered 350 or 1000 mg/kg/day. The applicant concludes that the effects were adverse in rat pups only at the dose level of 1000 mg/kg/day and proposes a NOAEL of 350 mg/kg/day for F1 development. However, similar findings, although to a lesser degree and not considered adverse, were already observed in the 350 mg/kg/day dose group. No effects were seen in the 50 mg/kg/day group which is the NOEL for this effect. Based on AUC-exposure data at the NOEL of 50 mg/kg/day, no safety margin to human exposure at the MRHD exists for this effect.

The significance of the specific effects on learning is not fully clear. However, impaired performance in a water-maze test for learning and memory was also reported for the approved TTC stabiliser tafamidis.

In addition, a study by Sousa et al. showed that 5-month-old TTR-null 129/Sv mice display spatial reference memory impairment when compared to age-matched wild-type mice in the water maze test (Sousa JC, Marques F, Dias-Ferreira E, Cerqueira JJ, Sousa N, Palha JA. Transthyretin influences spatial

reference memory. Neurobiol Learn Mem. 2007;88: 381–5). Due to its role in transport of thyroid hormone, the authors discussed that the cognitive impairment observed in 5-month-old TTR-null mice might ultimately be a consequence of hypothyroxinaemia during embryonic development. Slower acquisition in spatial learning and in altered synaptic function were also observed in a rat model of developmental thyroid hormone insufficiency (Gilbert & Sui, 2006).

Furthermore, TTR is also an important transporter of retinol which in addition is critical for brain development as well as learning and memory. Eight-week-old rats with a Vitamin A deficit during pregnancy, lactation and postweaning caused learning and memory impairment in the Morris water maze tests (Nali Hou & Lan Ren & Min Gong & Yang Bi & Yan Gu & Zhifang Dong & Youxue Liu & Jie Chen & Tingyu Li. Vitamin A Deficiency Impairs Spatial Learning and Memory: The Mechanism of Abnormal CBP-Dependent Histone Acetylation Regulated by Retinoic Acid Receptor Alpha. Mol Neurobiol (2015) 51:633–647 DOI 10.1007/s12035-014-8741-6).

Another study in rats showed that vitamin A deficiency started at weaning induced alteration of spatial memory in the simple Y-maze test at 13 weeks after weaning (Fabien Dumetz, Rachel Ginieis, Corinne Bure, Anaïs Marie, Serge Alfos, Véronique Pallet & Clémentine Bosch-Bouju (2022) Neuronal morphology and synaptic plasticity in the hippocampus of vitamin A deficient rats, Nutritional Neuroscience, 25:4, 779-790, DOI: 10.1080/1028415X.2020.1809877).

A possibility for that the observed impairment of learning and memory in rat pups by acoramidis could be considered as a pharmacologically related class effect, possibly due to the influence on transport of thyroid hormone and retinol by TTR or other transporters to the placenta and developing foetus or neonate, has not been fully addressed by the applicant. According to the applicant, as acoramidis is not a brain penetrant agent. The relevance of comparison to tafamidis, which does cross the blood brain barrier (Tsai 2023), remains uncertain. Regarding a class effect due to influence on thyroid hormone and retinol, acoramidis has not been tested in placental transfer studies. Moreover, the population studied in study AG10-301, ATTR-CM patients, are not in their reproductive years. In this population, there was no meaningful difference in the mean change from baseline of TSH over 30 months and no clinical meaningful difference in the incidence of thyroid adverse events.

Considering that the findings on learning and memory in rats are adverse only at exposures with sufficient safety margin (21-fold at the NOAEL) to the human exposure at the maximum dose, the clinical relevance is considered to be low. Also, adequate recommendation is proposed for use during pregnancy and in women of childbearing potential in section 4.6, as it reads there *"Acoramidis is not recommended during pregnancy and in women of childbearing potential not using contraception"*.

Information on the specific effects observed in the pre- and post-natal development study have been adequately included in section 5.3 of the SmPC. Furthermore, information on non-clinical data in the pregnancy subsection of section 4.6 of the SmPC also takes into account results from the pre- and post-natal development study.

No dedicated local tolerance studies were conducted as medicinal products intended for oral administration do not require such a study.

In an *in vitro* phototoxicity assay in mouse fibroblasts, acoramidis demonstrated a low potential for phototoxicity and unlikely to be a safety concern for humans. In silico analysis of acoramidis impurities suggested an unlikely potential for genotoxicity.

Acoramidis is unlikely to pose a risk to the aquatic, sediment and soil environments.

2.5.7. Conclusion on the non-clinical aspects

The nonclinical pharmacologic, pharmacokinetics, and toxicologic properties of acoramidis have been thoroughly evaluated and support the use of acoramidis in adult patients with transthyretin amyloidosis.

Acoramidis 356 mg film-coated tablets is not expected to pose a risk to the environment when used as prescribed.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

CHMP adopted a request for a routine GCP inspection on 22 February 2024. No specific concerns were identified by the assessment at the time of adoption of the inspection request. General triggers were used in the choice of the dossier and the sites involved. The conduct of study AG10-301 was inspected at two clinical investigator sites (one in New Zealand and one in Greece) and at the sponsor site (USA). No critical findings have been raised during the inspection, and the general conclusion of the inspectors was that the data reported in the clinical study report (CSR) can be used for the assessment of the marketing authorisation application.

- Tabular overview of clinical studies

Study Type	Study ID	Study Objective(s)	Study Design; Type of Control
Phase 1 Studies			
PK, PD, safety, tolerability	AG10-001	Evaluate the safety, tolerability, PK, PD, and food effect on the PK of single and multiple doses of acoramidis	Randomised, placebo-controlled, FIH, SAD, MAD, food effect XO
BE, safety, tolerability	AG10-003	Evaluate the BE, safety and tolerability of 2 formulations of acoramidis (single 400 mg [‘high strength’] tablet vs 2 × 200 mg tablets)	Randomised, OL, 2-sequence, 2-way XO
PK, safety, tolerability	AG10-004	Compare the PK, safety, and tolerability of acoramidis at 2 different doses in Japanese and non-Japanese participants	Randomised, OL, single dose, 2-way XO
PK, PD, safety, tolerability	AG10-005	Evaluate the safety, tolerability, PK, and PD of single, supratherapeutic doses of acoramidis	Randomised, placebo-controlled, SAD, supratherapeutic doses
ADME safety, tolerability	AG10-007	Assess the ADME, mass balance, safety and tolerability of oral [^{14}C]- acoramidis	OL, single dose
DDI safety, tolerability	AG10-008	Assess the potential inhibitory effect of acoramidis on OAT1 and OAT3; assess the safety and tolerability of multiple doses of acoramidis when administered with a single dose of adefovir or oseltamivir	OL, 2-part, 2- period, uncontrolled
Food effect (PK), safety, tolerability	ALXN2060-HV-101	Determine effect of a high-fat, high-calorie meal on the PK of acoramidis and its metabolite; safety and tolerability of	Randomised, OL, 2-period, 2- sequence, single dose, 2-way XO

		acoramidis	
Phase 2 Studies			
Safety, tolerability, PK, PD	AG10-201	Evaluate the safety, tolerability, PK, and PD of acoramidis	Randomised, double-blind, placebo- controlled, parallel group, dose-ranging
Long term safety, tolerability, PK, PD	AG10-202	Evaluate the long-term safety, tolerability, PK and PD of acoramidis	OLE and safety evaluation
Phase 1 Studies			
Efficacy, PD, safety, tolerability	AG10-301	Evaluate the efficacy, PD, safety and tolerability of acoramidis versus placebo	Randomised, double-blind, placebo- controlled
Long term safety, tolerability, efficacy, PD	AG10-304	Evaluate the long-term safety, tolerability, efficacy, PD of acoramidis	OLE and safety evaluation
Efficacy, safety, tolerability, PD	ALXN2060-TAC-302	Evaluate the efficacy, safety, tolerability, and PD of acoramidis in patients in Japan	OL, 2-part, uncontrolled
Expanded Access Use			
Expanded access use	AG10-999	Expanded Access for a single patient	OL, uncontrolled

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BE = bioequivalence; FIH = first in human; MAD = multiple ascending dose; OL = open-label; OLE = open label extension; PD = pharmacodynamics; PK = pharmacokinetics; SAD = single ascending dose; XO = crossover

In the clinical programme the following analytical methods were validated and used as listed in the table below.

Methodology	Objective(s)
LC-MS/MS	Acoramidis and acoramidis-acylglucuronide concentration in human plasma and urine Adefovir, oseltamivir and oseltamivir carboxylate concentrations in human plasma
Immunoturbidimetric procedure	Prealbumin (TTR or thyroxin-binding prealbumin; Roche Diagnostics c702/ c503 or Abbott Architect system)
ELISA kits (Aviva Systems Biology)	Prealbumin in Study AG10-001
Fluorescent Probe Exclusion Assay (FPE)	TTR Stabilisation in Serum
Western Blot	TTR Stabilisation in Plasma (the WB analysis was used to confirm the FPE assay results)
Liquid scintillation counting	Analyses of total radioactivity in plasma, whole blood, urine, and, if applicable, emesis

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Results from pharmacokinetic studies AG10-001, AG10-005, AG10-007 and AG10-003 generally indicate a consistency on acoramidis t_{max} across the all the dose levels tested, as single and multiple

dose administration of acoramidis. Moreover, there was also comparable exposure (AUCs and C_{max}) across the studies.

Following oral administration of single ascending doses of acoramidis (50, 150, 300 and 800 mg), there was a rapid absorption of the drug, with median plasma t_{max} values ranging from 0.75 to 1 hour across dose levels. T_{max} individual values ranged from 0.5 to 3.0 hours across the four dose levels. Following oral administration of multiple ascending doses of acoramidis (100, 300 and 800 mg), the drug also showed a rapid absorption, with median plasma t_{max} values ranging from 0.75 to 1.1 hour across the three dose levels for multiple dose day 1 and ranging from 0.5 to 1.0 hour for multiple dose day 12 (steady state condition). Steady state for acoramidis was reached by day 10.

Following oral administration of single ascending doses of acoramidis (50, 150, 300 and 800 mg), exposure parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) for plasma acoramidis were lower than dose proportional (factor increases in dose of 1:3:6:16 produced increases of approximately 1:1.7:2:4.3 in AUC_{0-t} and AUC_{0-inf}, and 1:1.6:2.1:5.2 in C_{max}). Following oral administration of multiple ascending doses of acoramidis (100, 300 and 800 mg) resulted in 1.3 to 1.6-fold accumulation of the compound based on the mean accumulation ratios for plasma acoramidis C_{max} at steady state (day 12) and that on day 1 of dosing. Inter-individual variability was low, with a geometric %CV of 21.2% for AUC_{tau} at steady state with 800 mg acoramidis HCl q12h dosing for 12 days.

Following oral administration of supratherapeutic single ascending doses of acoramidis (1200, 1600 and 2000 mg), there was a rapid absorption, with a median plasma t_{max} value of 1 hour across dose levels. T_{max} individual values ranged from 0.5 to 2.0 hours across the three dose levels. A saturation of exposure was observed at doses between 800 mg and 1200 mg acoramidis HCl.

Based on results from mass balance study, acoramidis was also rapidly absorbed following a single dose administration (~450 µCi) [^{14}C]-acoramidis), with a median plasma t_{max} value of 0.75 hours. T_{max} individual values ranged from 0.5 to 1.0 hours. Considering results from total radioactivity in urine, it is expected that at least 68% of a single 800 mg acoramidis dose is absorbed.

Based on results from bioequivalence study, there was a rapid acoramidis absorption following a single dose administration (as 1 x 400 mg and 2 x 200 mg as acoramidis HCl), with a median plasma t_{max} value of 0.75 hours. T_{max} individual values ranged from 0.5 to 3.0 hours.

Based on caco-2 *in vitro* assays, acoramidis was identified as an efflux substrate.

In vitro studies using MDCK-II cells treated to express BCRP indicated that acoramidis is a substrate for BCRP, but with no indication of saturation at concentrations up to 100 µM. *In vitro* studies using MDCK-MDR1 cells indicated that acoramidis is not a clinically relevant substrate as defined by the FDA (FDA, 2020) and EMA Guidance (EMA, 2012) for human P-gp and that it does not inhibit P-gp.

Acoramidis is an amphoteric compound, with pKa values of ~4.16 (pyrazole) and ~4.13 (carboxylic acid). As described in Section 3.2.S.1.3 and Section 3.2.P.2.1, the solubility of acoramidis HCl is pH dependent with a solubility of 5.63 mg/mL at a pH of 1.2 and 1.14 mg/mL at a pH of 6.8. The 712 mg dose is not completely soluble in ≤ 250 mL of aqueous media over the physiologically relevant pH range of 1.2 to 6.8, and thus acoramidis is classified as a low solubility compound based on the International Council for Harmonisation M9 BCS criteria. According to the applicant, the permeability classification for acoramidis in the BCS system has not been established due to efflux observed in permeability assays. In the Caco-2 permeability assay, the permeability results for acoramidis in the A→B direction for concentrations of 1, 10, and 50 µM were 0.04 ± 0.01 x 10^{-6} cm/s, 0.04 ± 0.00 x 10^{-6} cm/s, and 0.07 ± 0.01 x 10^{-6} cm/s, respectively. The efflux ratios were 421, 347, and 181 for concentrations of 1, 10, and 50 µM, respectively. The applicant has concluded that because passive transport is required to establish the BCS permeability classification using the Caco-2 assay, there are no data available to definitively assign a BCS permeability classification.

However, and according to ICH M9 Guideline, permeability may be estimated based on results from mass balance study using urine recovery data as the sum of parent drug (unchanged), Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in faeces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in faeces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in faeces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.

The proposed wording for section 5.2 of the SmPC regarding “Absorption” is supported by data and it is agreed:

“Following oral administration, acoramidis is rapidly absorbed and peak plasma concentration of unchanged acoramidis is usually achieved within 1 hour. Increases in plasma concentration were observed for acoramidis doses from 44.5 mg once daily (QD) to 712 mg QD. Plasma exposures appeared to saturate at acoramidis doses over 712 mg to 1068 mg. A steady state is achieved by 10 days of dosing with 712 mg twice daily, and repeated dosing results in minor (approximately 1.3 to 1.6-fold) accumulation of acoramidis.”

Bioavailability

The absolute bioavailability after oral administration of acoramidis has not been investigated in humans. Nevertheless, absolute oral bioavailability values were determined in animal species mouse (30.5%), rat (59.7%), dog (39.5%), and monkey (49.4%).

Bioequivalence

In the bioequivalence study AG10-003 performed under single dose on fasting conditions, the 400 mg acoramidis tablet to be used in the pivotal Phase 3 study was tested *versus* two 200 mg acoramidis tablets used in the early studies.

The overall total exposure (AUC_{0-t} and AUC_{0-inf}) to acoramidis was similar following both drug regimens. Peak exposure (C_{max}) to acoramidis was lower following administration of ‘high strength’ (one × 400 mg) acoramidis HCl than two tablets of 200 mg acoramidis HCl. The arithmetic mean elimination $t_{1/2}$ and median T_{max} were comparable following the administration of both formulations.

The early tablet formulation 50 and 200 mg was used in the studies AG10-001, AG10-004, AG10-005, AG10-201 and AG10-999 (expanded access for a single patient). Both formulations were used in the studies AG10-003 and AG10-202 (extension of study AG10-201).

Influence of food

The influence of food (high fat high caloric) on the pharmacokinetics of acoramidis was tested in Study AG10-001 (200 mg + 2 x 50 mg) and ALXN2060-HV-101 (two × 400 mg tablets). On fasting condition, it was observed a higher C_{max} and a earlier T_{max}. Moreover, it was noted that in Study AG10-001, AUC derived from fasting condition was 20% lower in comparison to fed condition, whereas in study ALXN2060-HV-101, AUC derived from fasting condition was 7% higher in comparison to fed condition.

Distribution

In vitro protein binding of acoramidis in human plasma was 96.5% at 10 µM and 96.3% at 50 µM. In the human ADME study, the whole blood:plasma TRA partitioning ratios ranged from 0.49 to 0.52 up to 24 hours postdose, suggesting that there was little to no partitioning of acoramidis-related radioactivity in the cellular fraction of whole blood.

The $V_{z,ss}/F$ of acoramidis was 654 L after administration of 800 mg acoramidis HCl q12h for 12 days to HAV.

After a single dose of 800 mg (~450 µCi) [^{14}C]-acoramidis HCl oral suspension to HAV, the mean V_z/F for acoramidis in plasma was 230.7.

The proposed wording for section 5.2 of the SmPC regarding “Distribution” is supported by data and it is agreed:

“The apparent steady state volume of distribution of 712 mg acoramidis dosed twice daily is 654 litres.”

Elimination

In the mass balance study AG10-007, a total dose of 800 mg (~450 µCi) [^{14}C]-acoramidis HCl on the form of oral suspension was administered. A dose level of 800 mg acoramidis HCl was selected for this study once it was expected to provide a well-characterised PK profile at a safe and well-tolerated dose. Moreover, the administered 800 mg dose corresponds to the recommended oral dose (BID) for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). No issues related to a decrease on the oral bioavailability are expected following administration on the form of suspension in comparison to tablets.

A total of 102% of total radioactivity was recovered (urine and faeces). Based on results from mass balance study AG10-007, after a single dose of 800 mg (~450 µCi) [^{14}C]-acoramidis HCl oral suspension, approximately 34% of the dose was recovered in faeces (approximately half as unchanged drug and half as metabolites), and approximately 68% of the dose was recovered in the urine. Based on urinary concentrations, the percent of unchanged acoramidis in the urine was approximately 8% and the percent of acoramidis-AG metabolite was 30.8%. Based on radioactivity metabolite profiling, the percent of unchanged acoramidis in the urine was approximately 10% and the percent of acoramidis-AG metabolite was 37%. Results are concordant.

Results from SAD/MAD study AG10-001 indicate an increase of Cl/F, V/F and Cl_r with increasing dose, following both single and multiple dose administration. However, no increase on the elimination half-life was observed, with a general mean of approximately 27 h following multiple dose administration. Increase of Cl/F and V/F may be due to a decrease in the bioavailability (F) of acoramidis. However, such issue is not discussed by the applicant, as well as the reasoning for the increase of renal clearance.

The proposed wording for section 5.2 of the SmPC regarding “Elimination and Excretion” is supported by data and agreed:

“The terminal half-life of acoramidis is approximately 27 hours after a single dose. At steady state, the apparent oral clearance of acoramidis is 15.6 L/h.

After administration of a single oral dose of [^{14}C]-acoramidis to healthy adult volunteers, approximately 34% of dose radioactivity was recovered in faeces (acoramidis being the major component) and approximately 68% was recovered in urine. The percent of unchanged acoramidis in the urine was < 10%.”

Pharmacokinetics of metabolites

The major metabolite of acoramidis is acoramidis-β-D-glucuronide, with about 1/3 activity. Plasma pharmacokinetics is somewhat similar with acoramidis, but with a less pronounce initial decrease from 1h to 2h post dose. In study AG10-001, C_{max} of 9820 ng/ml, a T_{max} of 1.2 h, and a C_{trough} of 917 ng/ml were derived for acoramidis-β-D-glucuronide following multiple doses of 800 mg acoramidis, on day 12 (steady state).

Exposure parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) for plasma AG10-β-D-glucuronide were about dose proportional.

Consequences of possible genetic polymorphism

No information is provided.

Dose proportionality and time dependencies

Following single ascending dose administration of acoramidis HCl in fasting conditions (Study AG10-001), a non-linear relationship with dose was observed for acoramidis AUC_{0-inf} and C_{max}. For AUC_{0-t}, a linear but non-proportional (less than proportional) relationship with dose was observed. For acoramidis exposure parameters AUC_{0-t}, AUC_{0-inf}, and C_{max}, factor increases in dose of 1:3:6:16 produced increases of approximately 1:1.7:2:4.3 in AUC_{0-t} and AUC_{0-inf} and 1:1.6:2.1:5.2 in C_{max}.

Following q12h doses of acoramidis HCl for 12 days, a non-proportional (less than proportional) relationship with dose was concluded for plasma acoramidis PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} following multiple oral doses of acoramidis HCl in the 100 to 800 mg range.

Additionally, from Study AG10-005 it was observed that following administration of single oral doses of 1200 to 2000 mg acoramidis HCl, overall exposure to plasma acoramidis (geometric mean AUC_{0-t}, AUC_{0-24}, and AUC_{0-inf}) and peak exposure (geometric mean C_{max}) appeared to increase with increasing dose of acoramidis HCl from 1200 to 1600 mg, but not from 1600 to 2000 mg. Using also data from the AG10-001 study (50, 150, 300, and 800 mg acoramidis HCl), plasma C_{max} appeared to increase in a less than dose-proportional manner following administration of single oral doses of 50 to 2000 mg acoramidis.

Steady state was attained by day 10 following administration of multiple oral doses of acoramidis. Repeated dosing resulted in approximately 1.3- to 1.6-fold accumulation of the compound based on the mean accumulation ratios for plasma acoramidis C_{max} at steady state (day 12) and that on day 1 of dosing. Plasma concentration 12h post dose increased from 1780 ng/ml at day 1 to 2510 ng/ml at day 12 (Study AG10-001 MAD, 800 mg acoramidis).

Intra- and inter-individual variability

Intra- and inter-individual variability are considered limited.

Pharmacokinetics in the target population

In Study AG10-201 and Study AG10-202, both performed with patients, the acoramidis pre-dose levels (2439 ng/ml and ~2300 ng/ml) are similar to the C_{trough} findings from study AG10-001 performed with healthy subjects. In Study AG10-201, plasma levels 1h post-dose were apparently somewhat higher (15641 ng/ml) compared with the ones from healthy subjects. It is noted that the decrease in acoramidis plasma concentration from 1h to 2h (9326 ng/ml) post dose is less pronounced.

The pre-dose levels of acoramidis acylglucuronide compared with healthy subjects apparently are higher (2126 ng/ml and ~3000 ng/ml), however with higher SD and CV. Similarly, in study AG10-201 the acoramidis acylglucuronide plasma levels 1h post-dose was higher in patients (17064 ng/ml).

In study AG10-301 the acoramidis pre-dose levels ranged from 2358 ng/ml to 2941 ng/ml. The only 1-hour post-dose level measured at day 28 (11028 ng/ml) was lower than the finding in study AG10-201. For acoramidis acylglucuronide compared with healthy subjects, again higher pre-dose values are reported (2763 ng/ml - 4792 ng/ml). The mean acoramidis acylglucuronide 1h post-dose value was 14297 ng/ml.

Therapeutic window

Based on results from pre-clinical and clinical studies, the applicant has concluded that acoramidis has a wide therapeutic window based on the proposed posology of acoramidis 712 mg (two tablets, 356 mg) (800 mg acoramidis HCl) orally, twice daily.

Special populations

Except for a dedicated study comparing the pharmacokinetics of acoramidis between Japanese and non-Japanese healthy adult volunteers, the effect of sex, ethnic factors, weight, age and renal function were addressed by PopPK analysis. The applicant is however asked to complete the intended table about the inclusion of older subjects in the PK trails.

Impairment Renal Function

The applicant has adequately justified why a dedicated pharmacokinetic study in subjects with decreased renal function was not performed. Justification is in line with EMA Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014). Moreover, in the population modelling, which included data from patients enrolled in phase 2 and/or phase 3 studies with decreased renal function (Cl_{CR} values from 25.4 to 89 mL/min, corresponding from severe to mild renal impairment patients), the final popPK model did not include renal function as a covariate. Therefore, popPK model found no significant differences in the pharmacokinetics of acoramidis based on renal function.

The lack of data from a dedicated pharmacokinetic study in subjects with decreased renal function was not reflected in the original proposed SmPC. The applicant had only included a summary of findings regarding special populations in section 5.2 (Specific Populations) of the SmPC as follow:

“No clinically significant differences in the pharmacokinetics of acoramidis were observed based on age, race/ethnicity (including Japanese and non-Japanese), sex, or renal impairment.”

After being requested on D120 LoQ, the applicant has proposed the following sentence for SmPC section 5.2 (Special populations):

“A dedicated renal-impairment study was not conducted because acoramidis is not substantially eliminated by the renal route, and the main metabolite (acoramidis-AG) has no clinically relevant contribution to pharmacological activity. The population PK model predicted that renal function did not affect steady state plasma acoramidis concentrations.”

Nevertheless, on D180 there were still concerns on the contribution of acoramidis-AG metabolite to the pharmacological activity and the impact of renal impairment on the accumulation of plasma acoramidis-AG and consequently on the potential inhibition of acoramidis glucuronidation and overall pharmacological activity.

After the applicant's further clarification on the above issues, it was included in section 5.2 (Special populations) of SmPC the suggested sentence addressing the potential impact of renal impairment in the pharmacokinetics of acoramidis, as below:

"A dedicated renal-impairment study was not conducted because acoramidis is not substantially eliminated by the renal route. However, despite the main metabolite (acoramidis-AG) having no clinically relevant contribution to pharmacological activity in the studied population, data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis. Clearance of the acoramidis metabolite acoramidis-AG might be affected by severe renal impairment resulting potentially in higher systemic exposure of acoramidis-AG. While this potential increase in acoramidis-AG exposure is not expected to have a clinically meaningful contribution to pharmacologic activity. Hence, acoramidis should be used with caution in patients with severe renal impairment."

Impairment Hepatic Function

Acoramidis is not intended to be used in patients with impaired hepatic function. Therefore, in line with EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function, a dedicated pharmacokinetic study in subjects with impaired hepatic function was not performed.

The lack of data from a dedicated pharmacokinetic study in subjects with impaired hepatic function is reflected in section 5.2 (Specific Populations) of the SmPC as follow:

"Acoramidis has not been studied in patients with hepatic impairment."

Moreover, as acoramidis is metabolised to a significant extent, reduced hepatic function is expected to affect its pharmacokinetics. Therefore, the applicant has revised sections 4.2 and 4.4 of the SmPC as below, which was accepted.

"*Acoramidis has not been studied in patients with hepatic impairment and therefore is not recommended for use in this population (see sections 4.4 and 5.2)*"

Gender

No clinically significant differences in the pharmacokinetics of acoramidis were observed based on gender, after testing this intrinsic factor in the popPK modelling.

This finding is reflected in section 5.2 (Specific Populations) of the SmPC as follow:

"No clinically significant differences in the pharmacokinetics of acoramidis were observed based on age, race/ethnicity (including Japanese and non-Japanese), sex, or renal impairment."

Ethnic Factors

Following single oral doses of acoramidis HCl (Study AG10-004), overall exposure to acoramidis, as measured by geometric mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$, and C_{max} was comparable between Japanese and non-Japanese participants for the 400 mg and 800 mg dose levels, with a proportionality factor of 1.0 to 1.2 between the 400 and the 800 mg dose levels. No clinically significant difference in the PK profile of acoramidis between Japanese and non-Japanese participants was observed in the study.

Moreover, no clinically significant differences in the pharmacokinetics of acoramidis were observed based on race, after testing this intrinsic factor in the popPK modelling.

This finding is reflected in section 5.2 (Specific Populations) of the SmPC as follow:

“No clinically significant differences in the pharmacokinetics of acoramidis were observed based on age, race/ethnicity (including Japanese and non-Japanese), sex, or renal impairment.”

Weight

No clinically significant differences in the pharmacokinetics of acoramidis were observed based on body weight, after testing this intrinsic factor in the popPK modelling. However, such information is not reflected in the SmPC.

Elderly

The pharmacokinetics of acoramidis was studied in healthy subjects and in patients with sparce sampling (studies AG10-201, AG10-202, and AG10-301) for the quantification of pre-dose levels. Across all studies performed with patients, all participants were in the range of 57 to 89.3 years. In these studies, a total of 84 subjects were in the range of 65 to 74 years, a total of 107 subjects were in the range of 75 to 84 years and a total of 18 subjects were > 85 years.

Population PK modelling tested age as a covariate. However, no clinically significant differences in the pharmacokinetics of acoramidis were observed based on this intrinsic factor.

This finding is reflected in section 5.2 (Specific Populations) of the SmPC as follow:

“No clinically significant differences in the pharmacokinetics of acoramidis were observed based on age, race/ethnicity (including Japanese and non-Japanese), sex, or renal impairment.”

Moreover, in section 4.2 (Posology and method of administration) of the SmPC it is stated that “No dose adjustment is required in elderly patients (≥ 65 years, see section 5.2).”

Paediatric population

A product-specific waiver, covering ATTR-CM and ATTR-PN, as ATTR-CM does not occur in any paediatric subset and clinical studies are not feasible in ATTR-PN paediatrics patients due to isolated cases of children affected by this condition, was granted on 8 October 2018 (P/0330/2018).

According to section 4.1 (Therapeutic indications) of the SmPC, acoramidis is only indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

The safety and effectiveness of acoramidis have not been established in paediatric patients.

Table 2: Number of older participants in clinical pharmacokinetic studies

PK Study	Number of Older Participants/Number Total Participants[a]		
	Age 65-74	Age 75-84	Age 85+
AG10-201	9/32 at 400 mg BID	6/32 at 400 mg BID	0/32 at 400 mg BID
	8/32 at 800 mg BID	6/32 at 800 mg BID	2/32 at 800 mg BID
AG10-202	25/47 at 800 mg BID	16/47 at 800 mg BID	4/47 at 800 mg BID
AG10-301[b]	42/140 at 800 mg BID	79/140 at 800 mg BID	12/140 at 800 mg BID

[a] Participants on placebo not included.
[b] For AG10-301, total number = number of participants in PK-PD substudy out of a total study participant number of 632.

Pharmacokinetic interaction studies

According to the applicant, no clinically relevant DDIs are expected.

In silico

PBPK model predicted a relatively weak to moderate changes in pravastatin and methotrexate exposure in the presence of steady state Acoramidis levels.

In vitro

From preclinical studies, an irreversible inhibition of CYP2C8 and CYP2C9 is reported (IC_{50} values of 76 µM and 100 µM, respectively). The unbound steady state plasma concentrations following multiple dose administration of 800 mg q12h is 1.51 µM, which is 50-fold and 66-fold lower than the IC_{50} values for CYP2C8 and CYP2C9, respectively, corresponding to a predicted inhibition of approximately 4% of CYP2C8 and 6% of CYP2C9. Given that a dedicated DDI clinical study was not performed, the following sentence was included in section 4.5 of the SmPC until robust DDI data are available:

“However, acoramidis was shown to be a weak inhibitor of CYP2C8 and CYP2C9 *in vitro*. No *in vivo* study has been performed. Therefore, concomitant CYP2C8 and CYP2C9 substrates with narrow therapeutic index should be used with caution.”

Following results from *in vitro* studies where a potential DDI was suggested by inhibition of human OAT1 (IC50 = 1.39 µM) and OAT3 (IC50 = 1.26 µM) by acoramidis, study AG10-008 was performed.

It is considered that study AG10-008 was appropriately designed. Potential maximum inhibition of transporters OAT1 and OAT3 was achieved through steady state acoramidis concentrations following the recommended posology of 800 mg BID, during 8 days (Part 1) and 9 days (Part 2). Study report shows in plots that acoramidis steady state (through concentration) was achieved within these administration periods.

Adefovir and oseltamivir carboxylate are recommended by the FDA as substrates for clinical DDI studies of OAT1 and OAT3, respectively (FDA, 2020).

Based on these results, no dose recommendations are needed for potential co-administration of acoramidis and OAT1 substrates.

In vivo

A clinical DDI study (AG10-008) was conducted in healthy volunteers to assess the potential inhibitory effect of acoramidis on OAT1 and OAT3 substrates, adefovir and oseltamivir carboxylate, respectively, when administered with a single dose of an OAT1 (adefovir) or OAT3 (oseltamivir) substrate. Acoramidis had minimal inhibitory effects on OAT1 and no inhibitory effects on OAT3 after oral administration of 800 mg acoramidis HCl q12h for 8 or 9 consecutive days.

The proposed wording for section 4.5 of the SmPC regarding “Interaction with other medicinal products and other forms of interaction” is supported by data and agreed:

“In a clinical study in healthy adult volunteers, following the administration of acoramidis (712 mg, twice daily), results showed < 1.2-fold increase in exposure of the organic anion transporter-1 (OAT1) substrate (adefovir), and no increase in exposure to OAT3 substrate (oseltamivir carboxylate).”

Moreover, and despite the marked pH dependent solubility of acoramidis in the physiological pH range, a dedicated *in vivo* DDI study with gastric acid reducing agents was not performed. The applicant has therefore included a suggested sentence in section 4.5 (Effect of other medicinal products on acoramidis) of the SmPC:

"*Effect of other medicinal products on acoramidis*

No dedicated in vivo drug-drug interaction study with gastric acid reducing agents was performed. Thus, the effect of gastric acid reducing agents on the pharmacokinetics of acoramidis is unknown. Despite the marked pH dependent solubility of acoramidis in the physiological pH range, no differences were observed in the pharmacodynamic marker (TTR stabilisation) between patients taking acid reducing agents and patients not taking acid reducing agents, in the phase III study".

Pharmacokinetics using human biomaterials

Protein binding

The method used to investigate the extent of acoramidis protein binding in plasma from Sprague Dawley rats, beagle dogs, cynomolgus monkeys, and humans is adequate and properly validated. Generally, a high protein binding was found across all species. Tested concentrations of 10 µM and 50 µM corresponds to 2923 ng/mL and 14616 ng/mL, respectively (MW of acoramidis is 292.31 g/mol). These concentrations are similar to acoramidis plasma concentrations C_{min} (2450 ng/mL) and C_{max} (12400 ng/mL) estimated for steady state following multiple oral dose administration (BID) of acoramidis HCl 800 mg in study AG10-001, which is the recommended posology.

No binding to erythrocytes is expected based on *in vitro* results. Tested concentrations of 0.1 µM (29.2 ng/mL) to 10 µM (2923 ng/mL) cover the expected range of free plasma concentrations of acoramidis in steady state following multiple oral dose administration (BID) of acoramidis HCl 800 mg (i.e. 88 ng/mL to 446 ng/mL based on C_{min} and C_{max} and assuming an unbound fraction of 3.6%).

The proposed wording for section 5.2 of the SmPC regarding "Distribution" is supported by data and agreed:

"*In vitro* binding of acoramidis to human plasma proteins is 96.4%. Acoramidis primarily binds to TTR."

Metabolism

In vitro

Both, *in vitro* metabolic stability assay of acoramidis with HLM and *in vitro* metabolite identification study of acoramidis in human hepatocytes indicated minimal CYP involvement in the metabolism of acoramidis. In human hepatocytes experiments, an acoramidis concentration of 10 µM was used, which is within the mean range of [0.302 to 1.527]µM found in study AG10-001 as $C_{min,ss}$ and $C_{max,ss}$ following multiple dose administration of 800 mg acoramidis HCl. The acoramidis concentration used in the experiment is therefore acceptable.

Moreover, a positive control, 7-ethoxycoumarin (7-EC) at 100 µM, was incubated concurrently to assess Phase I and Phase II metabolic activities, respectively, of hepatocytes, which is acceptable. Acoramidis was also shown to be chemically stable in hepatocyte incubation media after the 4-hr incubations.

In vitro assays also concluded that acoramidis-β-D-glucuronide was the predominant metabolite and that the major contribution to its formation appears to be from UGT2B7, followed by UGT1A9 and UGT1A1. No information regarding inter-conversion of glucuronide metabolite to parent is provided.

Nevertheless, given that acoramidis-AG accounts for only 30.8% of total radioactivity of human urine, it was estimated that none of the individual UGT isozymes contributes > 20% to acoramidis-AG formation *in vivo*. Therefore, a clinically relevant DDI is not expected for any of the single UGT enzymes involved in catalysis of the acoramidis-AG pathway. Furthermore, only 7.6% of the circulating TRA in plasma following administration of [^{14}C]-acoramidis was associated with plasma acoramidis-AG

AUC (Study AG10-007), which is one-third as active as the parent, thus a clinically relevant DDI is not expected for circulating acoramidis-AG.

Acoramidis was tested in the concentration range of 0.15 to 150 µM as inhibitor of human CYP450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and CYP2D6, and in the concentration range of 1.1 to 1100 µM as inhibitor of human CYP450 CYP3A4/5. The range of concentrations cover more than 50 times the mean unbound plasma $C_{max,ss}$ following multiple 800 mg acoramidis HCl dose ($50*C_{max,ss,unbound}$ = 76.36 µM) and also the potential intestinal concentration (973 µM) determined as the single dose of acoramidis (711 mg) divided by 250 mL (volume of the glass of water) for CYP3A4 evaluation.

Acoramidis did not significantly inhibit any of the seven major human CYP450 isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9, CYP2D6 [IC_{50} > 150 µM], and CYP3A4/5 [IC_{50} > 1100 µM]). However, acoramidis caused irreversible metabolism-dependent inhibition of CYP2C8 and CYP2C9 after a 30-minute preincubation with NADPH (IC_{50} values of 76 µM and 100 µM, respectively).

In vitro assays have also concluded no evidence of inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A6, and UGT2B15 by acoramidis, in the concentration range of [0.2 – 200]µM and have concluded to inhibit UGT1A9 to a maximum of 35% (IC50 >150 µM) and UGT2B7 to a maximum of 21% (IC50 >200 µM). The range of acoramidis concentrations used in these experiments cover the range from unbound $C_{min,ss}$ (0.302 µM) to more than 50 times the mean unbound plasma $C_{max,ss}$, following multiple 800 mg acoramidis HCl dose.

Acoramidis was shown to be not an inducer of CYP1A2, CYP2B6, and CYP3A4 in the acceptable concentration range of 0.15 to 150 µM. Additionally it is also estimated that induction of UGT2B7 and UGT1A9 by acoramidis is unlikely to cause any potential clinically relevant DDI, given the low contribution of these enzymes to acoramidis metabolism.

Regarding transporters, it was concluded that acoramidis is not a substrate for OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, or BSEP, but is a substrate for OAT1 and BCRP, in the acceptable concentration range of 0.3 to 30 µM. For OAT1, the K_m value was determined to be 28.5 µM (corresponding to 8331 ng/mL) with a V_{max} of 45.4 pmol/min/cm^2, and for BCRP, the K_m value was > 100 µM (corresponding to 29231 ng/mL), and the V_{max} value could not be determined. Given the high K_m values and the relatively low amounts of intact acoramidis excreted in urine, no clinically significant DDIs are anticipated for acoramidis as a substrate of these transporters.

No statistically significant inhibition of transport mediated by human OCT1, OCT2, OATP1B1, OATP1B3, MATE2-K, BSEP, P-gp, or BCRP was observed *in vitro* by acoramidis at a concentration of 30 µM. Therefore, no clinically relevant DDIs with substrates of these transporters are anticipated. However, acoramidis inhibited *in vitro* transport mediated by OAT1, OAT3, and MATE-1, with IC_{50} values estimated to be 1.39 µM, 1.26 µM, and 178 µM, respectively. Based on the calculated $I_{max,u}/IC_{50}$ values, there may be a potential for clinical DDIs with OAT1/OAT3 substrates such as loop diuretics (e.g., furosemide) which are the most common co-medication class used to manage heart failure in patients with ATTR-CM.

Regarding the potential inhibition by acoramidis-AG, at a concentration of 20 µM no statistically significant inhibition was seen for OCT2 or MATE2-K mediated transport, but was seen for transport mediated by OAT1 (22.8%), OAT3 (63.5%), and MATE1 (32.3%). IC50 was then determined only for OAT1 (36.7 µM). All the *in vitro* experiments used as transporter substrates the ones defined by FDA at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-1.

Given the potential inhibition effect of acoramidis and acoramidis-AG on OAT1 and OAT3, a clinical DDI study (AG10-008) was conducted in HAV to assess the potential inhibitory effect of acoramidis (and acoramidis-AG) on OAT1 and OAT3 substrates.

The proposed wording for section 4.5 of the SmPC regarding “Interaction with other medicinal products and other forms of interaction” is supported by data and agreed:

“Acoramidis is a substrate for breast cancer resistance protein (BCRP). No drug-drug interaction with co-administered BCRP substrates or inhibitors is anticipated at clinically relevant concentrations.

Acoramidis inhibits OAT1, OAT3, and MATE1 (multidrug and toxin extrusion). No clinically relevant drug-drug interaction is anticipated for co-administered OAT1, OAT 3 and MATE1 substrates.

Acoramidis is unlikely to cause any clinically relevant Cytochrome P450-dependent drug-drug interactions.

Acoramidis is unlikely to cause any clinically relevant UDP-glucuronosyl transferase-dependent drug-drug interactions.”

Exposure relevant for safety evaluation

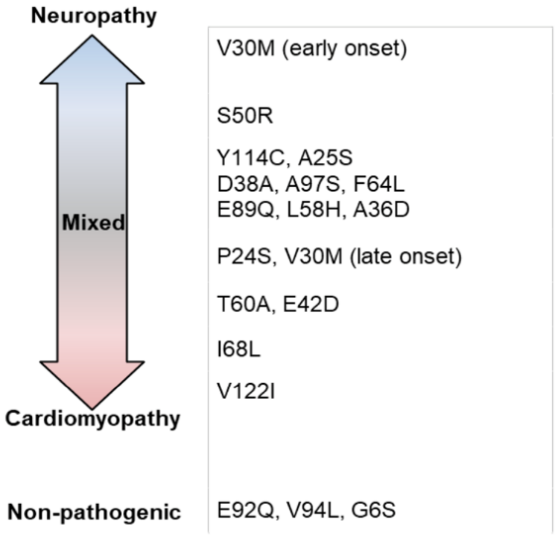
In the phase 1 studies 165 subjects were exposed to acoramidis. 38 subjects were exposed to 800 mg acoramidis multidose.

2.6.2.2. Pharmacodynamics

Mechanism of action

Acoramidis is an oral, potent, high-affinity TTR stabiliser that acts to inhibit the dissociation of tetrameric TTR. It was rationally designed, informed by human genetics and structural biology, to mimic the stabilizing effects of T119M, a disease-protective gene variant (Miller et al., 2018), through a unique mode of binding to TTR. With respect to plasma protein binding, acoramidis has a higher free fraction, has higher binding affinity for both thyroxine binding sites, and employs a predominantly enthalpic binding mode involving hydrogen bonding, mimicking the T119M protective mutation’s mechanism of enhanced stabilisation. *In vitro* studies of acoramidis were focused on potency and specificity of binding to its target protein TTR. Evaluation was carried out to measure interactions at the binding sites shared with TTR’s natural ligand T4.

Figure 2: TTR Variant Phenotypes



Source: NC-363

In addition, interactions in the presence of plasma proteins (exogenously added or in plasma/serum) were tested to predict potency of the drug under physiological conditions. In addition to TTRwt, acoramidis was tested for cross reactivity and target engagement with TTRv of multiple genotypes and phenotypes (Figure 2).

Characterisation of the pharmacology and mechanism of action of acoramidis consisted of *in vitro* and *ex vivo* studies. Potency and selectivity of TTR stabilisation by acoramidis was investigated using purified TTR protein, serum and plasma samples from both healthy donors and ATTRv-CM participants harbouring TTRv. Animal models of ATTR do not reproduce the human phenotype (tissue deposition of fibrils) and therefore were not used for characterisation of acoramidis. For example, a mouse model that overexpresses the pathogenic TTRv V30M does not sufficiently recapitulate the polyneuropathy phenotype. Fibrillar TTR deposits, as in patients, are not detected in the animal model. Neurological impairments are not seen; although the deposition of TTR is strong and highly penetrant in the skin and gastrointestinal (GI) tract, it is less so in the target organ of interest, the peripheral nervous system. Thus, the characterisation of acoramidis utilised *in vitro* and pharmacodynamic measurements in serum from widely used, non-genetically modified laboratory animals rather than an animal model.

Acoramidis binding to purified TTR protein was tested by fluorescence polarisation, isothermal calorimetry (ITC), surface plasmon resonance (SPR) and microscale thermophoresis (MST), and in crystallographic studies. Evaluation of acoramidis binding to TTR in physiologic buffer shows a high binding affinity with occupancy of both T4 binding sites. The low dissociation rate constant of acoramidis from TTR, as measured by SPR, may indicate a potential for higher persistence of the acoramidis-TTR tetramer complex resulting in a longer lasting pharmacological effect. Study of co-crystallisation of acoramidis in complex with the TTRv V122I, and modelling studies with TTRwt, revealed that acoramidis sits deep within the inner cavity of the two T4 binding sites and forms two salt bridges with the charged Lys15 and Lys15' residues in the top end of the T4 binding site and two hydrogen bonds with Ser117 and Ser117' residues of adjacent monomeric subunits of TTR at the opposite end of the binding cavity. The latter observation is unique compared to other stabilisers and particularly important as it mimics the binding interactions between Ser117 and Ser117' seen in the T4 binding site of stabilizing rescue TTRv T119M in crystallographic studies.

Serum and plasma-based assays of acoramidis pharmacodynamics included measurements of acoramidis binding to TTR in two *in vitro* assays. The first assay, a highly sensitive and specific fluorescent probe exclusion (FPE) assay measures TTR target binding site occupancy in serum. FPE was tested in pooled samples from healthy adult volunteers and in individual samples from participants with ATTR-CM. The second *in vitro* system for testing TTR stabilisation in plasma incorporated acid mediated dissociation to accelerate the rate of TTR dimer/monomer formation and their subsequent quantitation by immunoblots; western blot (WB). The WB quantifies tetrameric TTR persistence under conditions of accelerated dissociation.

Primary pharmacology

Preclinical studies and *ex vivo* binding studies with serum samples from patients with ATTR have shown that acoramidis binds with higher affinity and greater selectivity than the natural ligand of TTR, T4, and other TTR stabilisers, including tafamidis, diflunisal, and tolcapone (Ji et al., 2023; Miller et al., 2018; Penchala et al., 2013). These studies also showed that acoramidis led to a concentration-dependent stabilisation of both wild-type and pathogenic TTR variants, and prevented the dissociation of the TTR tetramer into its constituent monomers (Penchala et al., 2013).

Studies AG10-001, AG10-005 and AG10-201 were multiple dose Phase 1 and Phase 2 studies in which the primary pharmacodynamics was evaluated and confirmed as well as the dose-effect relationship. These studies are further detailed in this assessment report in the 2.4.1 section.

Study AG10-202 was an Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201.

The primary objective of this study was to evaluate the long-term safety and tolerability of acoramidis administered to adult patients with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) in patients who completed the study AG10-201.

The secondary objectives of this study were: 1) to characterise the pharmacokinetics (PK) of acoramidis administered orally twice daily in subjects with symptomatic ATTR-CM, and; 2) to describe the pharmacodynamic (PD) properties of acoramidis as assessed by established assays of transthyretin (TTR) stabilisation, including fluorescent probe exclusion (FPE) assay and western blot (WB), and to describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM.

The PD of acoramidis were assessed by serum TTR levels as an in vivo PD biomarker and established assays of TTR stabilisation, including FPE assay, and WB. TTR stabilisation ex vivo parameters were summarised by visit. In addition, these parameters were plotted vs. plasma drug concentrations.

All subjects, regardless of genotype, showed increases in serum TTR observed values, change from baseline and percent change from baseline by day 14 and through subsequent time points (up to month 36). Mean and median serum TTR levels were over 20 mg/dL by day 14 and maintained through subsequent time points up to month 36.
The majority of subjects with ATTRv-CM had serum TTR levels <20 mg/dL at baseline.

- These subjects showed larger absolute and percent increases over baseline.
- The majority of these subjects reached normal levels of serum TTR by day 14, which were generally sustained through subsequent timepoints.

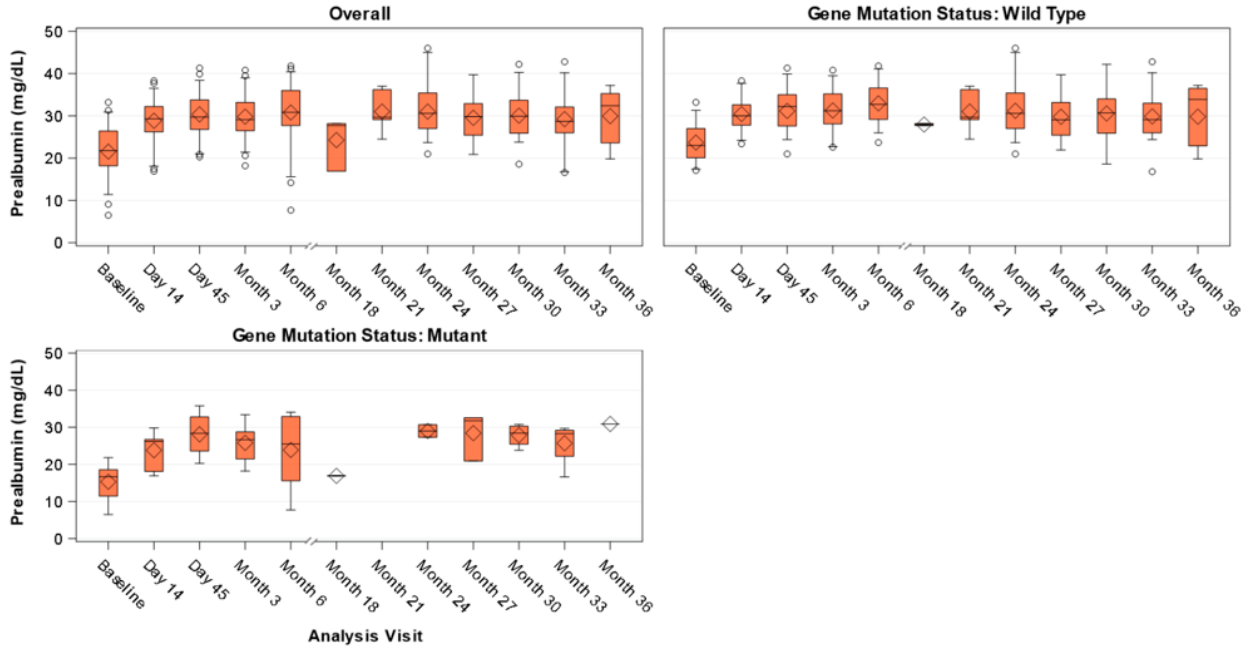
The FPE assay results show near-complete (≥90%) *ex vivo* stabilisation of TTR in most subjects from day 14 through month 36. The WB results were similar to those of the FPE, with near-complete TTR stabilisation at most timepoints from day 14 through month 36 in the majority of subjects.

Table 3: Percent Increase in Prealbumin by Visit and Gene Mutation Status (PD analysis Set)

Visit Percent Increase [n (%)]	Wild Type (N=35)	Mutant (N=12)	All Subjects (N=47)
Day 14 [n]	35	11	46
≥10%	30 (85.7)	11 (100)	41 (89.1)
≥25%	23 (65.7)	9 (81.8)	32 (69.6)
≥50%	3 (8.6)	7 (63.6)	10 (21.7)
Day 45 [n]	33	12	45
≥10%	30 (90.9)	12 (100)	42 (93.3)
≥25%	23 (69.7)	12 (100)	35 (77.8)
≥50%	7 (21.2)	9 (75.0)	16 (35.6)
Month 3 [n]	33	12	45
≥10%	30 (90.9)	10 (83.3)	40 (88.9)
≥25%	21 (63.6)	10 (83.3)	31 (68.9)
≥50%	5 (15.2)	10 (83.3)	15 (33.3)
Month 6 [n]	32	10	42
≥10%	30 (93.8)	9 (90.0)	39 (92.9)
≥25%	26 (81.3)	7 (70.0)	33 (78.6)
≥50%	7 (21.9)	6 (60.0)	13 (31.0)
Month 18 [n]	2	1	3
≥10%	1 (50.0)	1 (100)	2 (66.7)
≥25%	1 (50.0)	1 (100)	2 (66.7)
≥50%	0	0	0
Month 21 [n]	6	0	6
≥10%	5 (83.3)	0	5 (83.3)
≥25%	3 (50.0)	0	3 (50.0)
≥50%	0	0	0
Month 24 [n]	21	2	23
≥10%	19 (90.5)	2 (100)	21 (91.3)
≥25%	14 (66.7)	2 (100)	16 (69.6)
≥50%	5 (23.8)	2 (100)	7 (30.4)
Month 27 [n]	14	3	17
≥10%	10 (71.4)	3 (100)	13 (76.5)
≥25%	7 (50.0)	3 (100)	10 (58.8)
≥50%	0	3 (100)	3 (17.6)
Month 30 [n]	17	4	21
≥10%	13 (76.5)	4 (100)	17 (81.0)
≥25%	12 (70.6)	4 (100)	16 (76.2)
≥50%	2 (11.8)	3 (75.0)	5 (23.8)
Month 33 [n]	22	4	26
≥10%	17 (77.3)	4 (100)	21 (80.8)
≥25%	13 (59.1)	4 (100)	17 (65.4)
≥50%	2 (9.1)	3 (75.0)	5 (19.2)
Month 36 [n]	7	1	8
≥10%	5 (71.4)	1 (100)	6 (75.0)
≥25%	3 (42.9)	1 (100)	4 (50.0)
≥50%	0	1 (100)	1 (12.5)

Abbreviations: n = a subset of subjects; N = total number of subjects; PD = pharmacodynamics.
Note: Subjects may be counted in more than one category. Each subject's own pre-dose measurement is used for the % change calculation. At each visit, percentages are based on the number of subjects with non-missing assessment.
Day 1 prealbumin percent increase is not presented because by definition it is zero.
Source: Table 14.2.4.1

Figure 3: Box and Whisker Plots of Prealbumin Levels (mg/dL) by Visit (PD Analysis set)



Abbreviations: PD = pharmacodynamics.
Note: PD collection was not required for Months 9 and 12. In Protocol Amendment 3.0, PD collection at Month 15 and every 3 months after was added. However, due to COVID-19 related restrictions at the sites, there was no PD data collected at Month 15 and limited PD data collected at Months 18 and 21.
Source: Figure 14.2.4.1

ATTRibute-CM Trial (AG10-301) was a phase 3, randomised, double-blind, placebo-controlled study of the efficacy and safety of AG10 in subjects with symptomatic transthyretin amyloid cardiomyopathy.

The primary objective was to determine the efficacy of acoramidis in the treatment of participants with symptomatic ATTR-CM by evaluating the difference between the acoramidis and placebo groups in the combined endpoint of all-cause mortality, the cumulative frequency of CV-related hospitalisation, change from baseline in NT-proBNP, and change from baseline in 6MWD.

As a secondary objective, the applicant planned to assess the pharmacodynamic (PD) effects of acoramidis by assessing circulating prealbumin (transthyretin [TTR]) concentration as an *in vivo* biomarker of stabilisation.

Overall, the mean age at randomisation was 77 years and almost all participants (96.6%) were ≥ 65 years-of-age. Most participants were male (90.8%), White (87.9%), recently diagnosed with ATTR-CM (mean 1.2 years, range 0-10.1 years), and within NYHA Class II (72.7%). Ninety-nine participants (16.2%) were within NYHA Class III.

Participant demographics and stratification factors from IXRS are summarised overall and by treatment group for the mITT population (n = 611) in Table 4.

Table 4: Demographic and Baseline Characteristics of Analysis Population, mITT Population

	Acoramidis N = 409	Placebo N = 202	Overall N = 611
Age at Randomization (years)			
n	409	202	611
Mean (SD)	77.32 (6.474)	76.96 (6.739)	77.20 (6.560)
Median (Q1, Q3)	78.00 (73.00, 82.68)	77.89 (72.87, 81.90)	78.00 (73.00, 82.00)
Min, Max	50.3, 90.4	55.0, 90.0	50.3, 90.4
Age Category (years)			
< 65	12 / 409 (2.9%)	9 / 202 (4.5%)	21 / 611 (3.4%)
≥ 65 to < 78	186 / 409 (45.5%)	92 / 202 (45.5%)	278 / 611 (45.5%)
≥ 78	211 / 409 (51.6%)	101 / 202 (50.0%)	312 / 611 (51.1%)
Sex			
Male	374 / 409 (91.4%)	181 / 202 (89.6%)	555 / 611 (90.8%)
Female	35 / 409 (8.6%)	21 / 202 (10.4%)	56 / 611 (9.2%)
Ethnicity			
Hispanic or Latino	7 / 409 (1.7%)	4 / 202 (2.0%)	11 / 611 (1.8%)
Not Hispanic or Latino	391 / 409 (95.6%)	191 / 202 (94.6%)	582 / 611 (95.3%)
Not Reported	10 / 409 (2.4%)	6 / 202 (3.0%)	16 / 611 (2.6%)
Unknown	1 / 409 (0.2%)	1 / 202 (0.5%)	2 / 611 (0.3%)
Race			
American Indian or Alaska Native	0 / 409	1 / 202 (0.5%)	1 / 611 (0.2%)
Asian	10 / 409 (2.4%)	3 / 202 (1.5%)	13 / 611 (2.1%)
Black or African American	19 / 409 (4.6%)	10 / 202 (5.0%)	29 / 611 (4.7%)
Native Hawaiian or Other Pacific Islander	0 / 409	1 / 202 (0.5%)	1 / 611 (0.2%)
White	358 / 409 (87.5%)	179 / 202 (88.6%)	537 / 611 (87.9%)
Other	5 / 409 (1.2%)	1 / 202 (0.5%)	6 / 611 (1.0%)
Multiple races	2 / 409 (0.5%)	0 / 202	2 / 611 (0.3%)
Not reported	15 / 409 (3.7%)	7 / 202 (3.5%)	22 / 611 (3.6%)
BMI (kg/m^2)			
n	408	200	608
Mean (SD)	27.07 (3.798)	26.97 (3.694)	27.04 (3.761)
Median (Q1, Q3)	26.73 (24.46, 29.20)	26.55 (24.40, 29.26)	26.69 (24.45, 29.20)
Min, Max	18.1, 42.7	19.3, 40.0	18.1, 42.7

	Acoramidis N = 409	Placebo N = 202	Overall N = 611
Duration of ATTR-CM (years)			
n	408	202	610
Mean (SD)	1.24 (1.207)	1.12 (1.198)	1.20 (1.205)
Median (Q1, Q3)	0.83 (0.40, 1.70)	0.71 (0.30, 1.52)	0.79 (0.37, 1.64)
Min, Max	0.0, 10.1	0.0, 7.4	0.0, 10.1
NYHA Class			
I	51 / 409 (12.5%)	17 / 202 (8.4%)	68 / 611 (11.1%)
II	288 / 409 (70.4%)	156 / 202 (77.2%)	444 / 611 (72.7%)
III	70 / 409 (17.1%)	29 / 202 (14.4%)	99 / 611 (16.2%)
NAC ATTR Stage[a]			
I	241 (58.9%)	120 (59.4%)	361 (59.1%)
II	130 (31.8%)	66 (32.7%)	196 (32.1%)
III	38 (9.3%)	16 (7.9%)	54 (8.8%)
Stratification Factors (from IXRS)			
ATTRm-CM	39 / 409 (9.5%)	20 / 202 (9.9%)	59 / 611 (9.7%)
ATTRwt-CM	370 / 409 (90.5%)	182 / 202 (90.1%)	552 / 611 (90.3%)
NT-proBNP ≤ 3000 pg/mL	268 / 409 (65.5%)	133 / 202 (65.8%)	401 / 611 (65.6%)
NT-proBNP > 3000 pg/mL	141 / 409 (34.5%)	69 / 202 (34.2%)	210 / 611 (34.4%)
eGFR ≥ 45 mL/min/1.73 m^2	344 / 409 (84.1%)	173 / 202 (85.6%)	517 / 611 (84.6%)
eGFR < 45 mL/min/1.73 m^2	65 / 409 (15.9%)	29 / 202 (14.4%)	94 / 611 (15.4%)

Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRv-CM = variant ATTR-CM; ATTRwt-CM = wild-type ATTR-CM; BMI = body mass index; eGFR = estimated glomerular filtration rate; IXRS = Interactive Voice/Web Response System; Max = maximum; Min = minimum; mITT = modified intent-to-treat; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; Q = quartile; SD = standard deviation

Note: Percentages are of non-missing responses for categorical variables.

[a] NAC ATTR Stage: Stage I (NT-proBNP ≤ 3000 pg/mL and eGFR ≥45 mL/min/1.73 m^2), Stage II (NT-proBNP ≤ 3000 pg/mL and eGFR < 45 mL/min/1.73 m^2 or NT proBNP >3000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2), Stage III (NT-proBNP > 3000 pg/mL and eGFR < 45 mL/min/1.73 m^2).

Source: Table 14.1.4.1 and Table 14.1.4.10.

ATTR-CM type is summarised overall and by treatment group for the mITT population (n = 611) in Table 5.

Overall, 56 participants (9.2% of mITT Population) had ATTRv-CM, and 62.5% of these 56 participants were V122I. Overall, four participants were homozygotes for the TTR mutation (all V122I). Most participants, 75.9%, were diagnosed non-invasively without endomyocardial biopsy.

Table 5: ATTR-CM Diagnosis, mITT Population

	Acoramidis N = 409 n (%)	Placebo N = 202 n (%)	Overall N = 611 n (%)
Genetic Status			
Mutation	37 / 409 (9.0%)	19 / 202 (9.4%)	56 / 611 (9.2%)
Wild-type	371 / 409 (90.7%)	182 / 202 (90.1%)	553 / 611 (90.5%)
Unknown/patient refused	1 / 409 (0.2%)	1 / 202 (0.5%)	2 / 611 (0.3%)
Genotype of Mutation			
V122I	23 / 37 (62.2%)	12 / 19 (63.2%)	35 / 56 (62.5%)
T60A	3 / 37 (8.1%)	2 / 19 (10.5%)	5 / 56 (8.9%)
V30M	0 / 37	0 / 19	0 / 56
S77Y	0 / 37	0 / 19	0 / 56
T49A	0 / 37	0 / 19	0 / 56
L111M	0 / 37	0 / 19	0 / 56
E89Q	0 / 37	1 / 19 (5.3%)	1 / 56 (1.8%)
Other	11 / 37 (29.7%)	4 / 19 (21.1%)	15 / 56 (26.8%)
Zygosity of Mutation			
Heterozygote	31 / 37 (83.8%)	13 / 19 (68.4%)	44 / 56 (78.6%)
Homozygote	1 / 37 (2.7%)	3 / 19 (15.8%)	4 / 56 (7.1%)
Unknown	5 / 37 (13.5%)	3 / 19 (15.8%)	8 / 56 (14.3%)
Clinical Basis for Diagnosis			
Endomyocardial biopsy only	72 / 409 (17.6%)	43 / 202 (21.3%)	115 / 611 (18.8%)
Non-invasive only	315 / 409 (77.0%)	149 / 202 (73.8%)	464 / 611 (75.9%)
Endomyocardial biopsy and non-invasive	22 / 409 (5.4%)	10 / 202 (5.0%)	32 / 611 (5.2%)

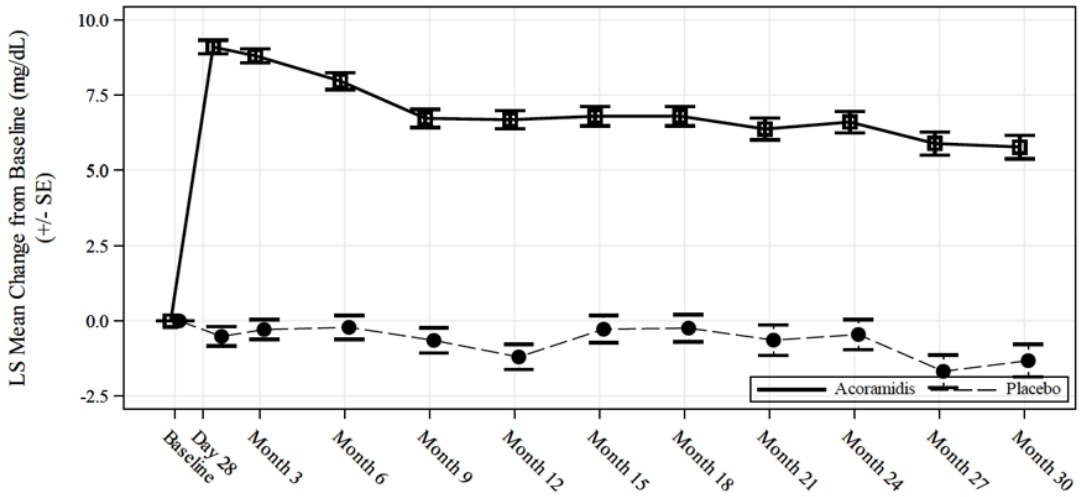
Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; mITT = modified intent-to-treat; n = number of participants in a particular category; N = total number of participants in the study arm
Note: Percentages are of non-missing responses for categorical variables.
Source: Table 14.1.5.1

The baseline assessment of endpoints are summarised overall and by treatment group for the mITT population in Table 6 (only TTR values were selected from the table).

Table 6: Baseline Assessments of Endpoints, mITT Population

	Acoramidis N = 409	Placebo N = 202	Overall N = 611
Serum TTR (mg/dL)			
N	406	199	605
Mean (SD)	23.0 (5.58)	23.6 (6.08)	23.2 (5.75)
Median (Q1, Q3)	23.0 (20.0, 27.0)	23.0 (20.0, 28.0)	23.0 (20.0, 27.0)
Min, Max	8, 48	6, 41	6, 48

Figure 4: Least Squares Mean (+/- SE) Change From Baseline in TTR Level (mg/DL) Over Time (with J2R), mITT Population



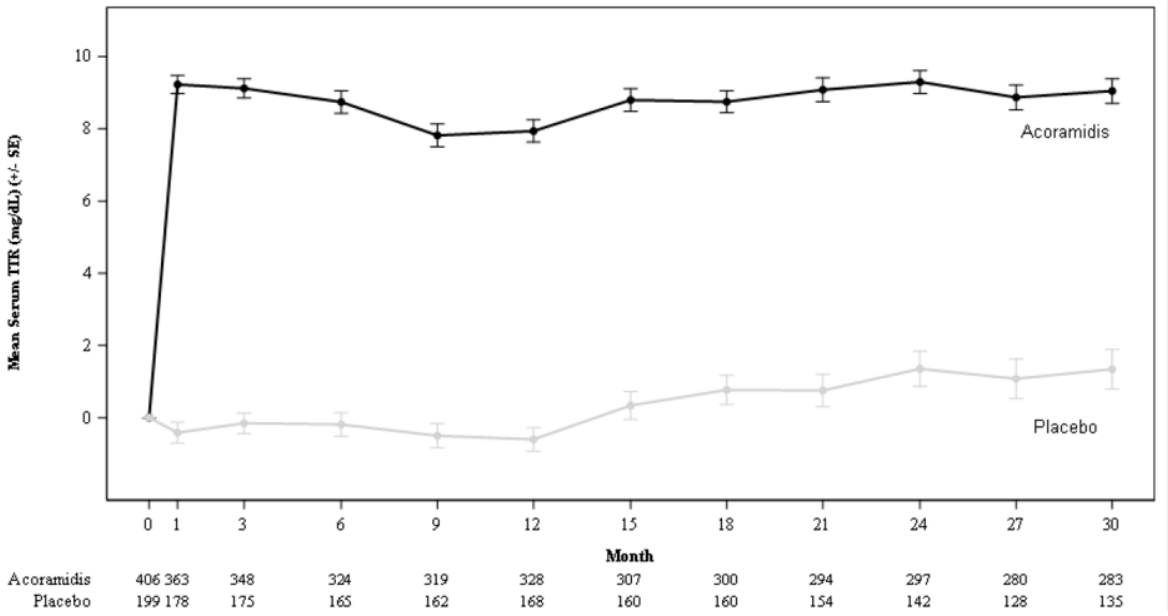
Acoramidis	406	367	359	353	357	378	376	381	387	398	391	397
Placebo	199	178	177	173	177	188	185	192	195	194	187	197

Abbreviations: ATTRv-CM = variant ATTR-CM; ATTRwt CM = wild-type ATTR-CM; eGFR = estimated glomerular filtration rate; J2R = Jump to Reference; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SE = standard error; TTR = transthyretin

Notes: The change from baseline in TTR level was analyzed using the MMRM with treatment group, visit, genotype (ATTRv-CM versus ATTRwt-CM), NT-proBNP level (≤ 3000 versus > 3000 pg/mL), eGFR level (≥ 45 versus < 45 mL/min/1.73 m^2) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study drug were imputed using the J2R method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values. Ns represent both observed and imputed data points.

Source: Figure 14.2.1.28

Figure 5: Line Plot of Change From Baseline in Mean Serum TTR Level (mg/DL) by Visit, mITT Population



Acoramidis	406	363	348	324	319	328	307	300	294	297	280	283
Placebo	199	178	175	165	162	168	160	160	154	142	128	135

Abbreviations: mITT = modified intent-to-treat; SE = standard error; TTR = transthyretin

Source: Figure 14.2.1.47d

A treatment effect for change from baseline in TTR level favouring acoramidis was observed early, from the first measurement at day 28. The increase in serum TTR level, observed in the acoramidis

treatment group, was sustained throughout the study, from day 28 through month 30. No increase in serum TTR level was observed for placebo (Figure 4). The line plot of change from baseline in observed mean serum TTR level by visit in the mITT Population is provided in Figure 5.

In both ATTRv-CM and ATTRwt-CM, a clinically meaningful treatment benefit in TTR level was observed in the acoramidis treatment group compared to placebo from the first measurement at day 28 through to month 30 (Table 14.2.1.52a).

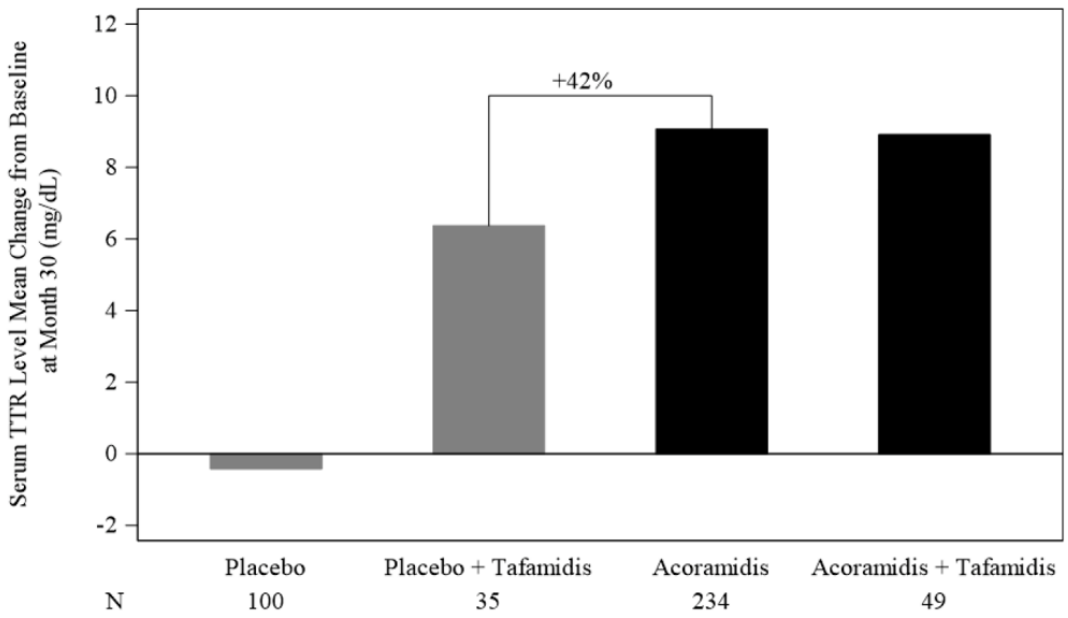
At baseline, 24.6% of participants in the acoramidis treatment group and 23.1% in the placebo group had TTR levels below the lower limit of the reference range (< 20 mg/dL). At month 30, in the mITT population, 2.8% of participants in the acoramidis treatment group and 14.1% in the placebo group remained below the reference range (Table 14.2.1.53).

In ATTRv-CM, at baseline, 55.3% of participants in the acoramidis treatment group and 65.0% in the placebo group had TTR levels below the lower limit of the reference range. At month 30, 4.2% of participants in the acoramidis treatment group and 42.9% in the placebo group remained below the reference range (Table 14.2.1.53a).

In ATTRwt-CM, at baseline, 21.5% of participants in the acoramidis treatment group and 18.4% in the placebo group had TTR levels below the lower limit of the reference range. At month 30, 2.7% of participants in the acoramidis treatment group and 12.5% in the placebo group remained below the reference range (Table 14.2.1.53a).

At month 30, the observed mean increase in TTR level was 9.07, 8.92, and 6.37 mg/dL in the acoramidis only, acoramidis plus tafamidis, and placebo plus tafamidis treatment groups, respectively. These findings demonstrate that (1) acoramidis only treatment resulted in a 42% greater increase in the mean change from baseline in serum TTR levels than did the addition of tafamidis to placebo, and (2) adding tafamidis to acoramidis did not have an incremental effect on serum TTR level (Figure 6).

Figure 6: Change from Baseline to Month 30 in serum TTR Level by Concomitant Tafamidis Groups, mITT Population



Abbreviations: mITT = modified intent-to-treat; N = number of participants with available serum TTR levels at baseline and Month 30; TTR = transthyretin
Source: Figure 14.2.3.14

Table 14.2.1.53a
Summary and Change from Baseline in TTR Level Category by Visit and by Genotype
mITT Population

ATTRwt-CM	Acoramidis (N=370)	Placebo (N=182)
Baseline		
TTR Level Category		
n	368	179
< 20 mg/dL	79 (21.5%)	33 (18.4%)
20 mg/dL – 40 mg/dL	288 (78.3%)	145 (81.0%)
> 40 mg/dL	1 (0.3%)	1 (0.6%)
Day 28		
TTR Level Category		
n	328	160
< 20 mg/dL	4 (1.2%)	36 (22.5%)
20 mg/dL – 40 mg/dL	291 (88.7%)	124 (77.5%)
> 40 mg/dL	33 (10.1%)	0
Month 3		
TTR Level Category		
n	314	159
< 20 mg/dL	13 (4.1%)	37 (23.3%)
20 mg/dL – 40 mg/dL	279 (88.9%)	122 (76.7%)
> 40 mg/dL	22 (7.0%)	0
Month 6		
TTR Level Category		
n	297	150
< 20 mg/dL	7 (2.4%)	28 (18.7%)
20 mg/dL – 40 mg/dL	268 (90.2%)	121 (80.7%)
> 40 mg/dL	22 (7.4%)	1 (0.7%)
n	29	16
< 20 mg/dL	2 (6.9%)	9 (56.3%)
20 mg/dL – 40 mg/dL	26 (89.7%)	7 (43.8%)
> 40 mg/dL	1 (3.4%)	0

Table 14.2.1.53a
Table 14.2.1.53a
Summary and Change from Baseline in TTR Level Category by Visit and by Genotype
mITT Population

ATTRwt-CM	Acoramidis (N=370)	Placebo (N=182)
Month 9		
TTR Level Category		
n	292	149
< 20 mg/dL	13 (4.5%)	35 (23.5%)
20 mg/dL – 40 mg/dL	261 (89.4%)	114 (76.5%)
> 40 mg/dL	18 (6.2%)	0
Month 12		
TTR Level Category		
n	298	157
< 20 mg/dL	10 (3.4%)	37 (23.6%)
20 mg/dL – 40 mg/dL	271 (90.9%)	118 (75.2%)
> 40 mg/dL	17 (5.7%)	2 (1.3%)
Month 15		
TTR Level Category		
n	279	147
< 20 mg/dL	6 (2.2%)	28 (19.0%)
20 mg/dL – 40 mg/dL	250 (89.6%)	118 (80.3%)
> 40 mg/dL	23 (8.2%)	1 (0.7%)
Month 18		
TTR Level Category		
n	272	150
< 20 mg/dL	9 (3.3%)	34 (22.7%)
20 mg/dL – 40 mg/dL	246 (90.4%)	111 (74.0%)
> 40 mg/dL	17 (6.3%)	5 (3.3%)

Table 14.2.1.53a
Summary and Change from Baseline in TTR Level Category by Visit and by Genotype
mITT Population

ATTRm-CM	Acoramidis (N=39)	Placebo (N=20)
Month 21		
TTR Level Category		
n	29	12
< 20 mg/dL	0	8 (66.7%)
20 mg/dL – 40 mg/dL	27 (93.1%)	4 (33.3%)
> 40 mg/dL	2 (6.9%)	0
Month 24		
TTR Level Category		
n	28	10
< 20 mg/dL	2 (7.1%)	7 (70.0%)
20 mg/dL – 40 mg/dL	22 (78.6%)	3 (30.0%)
> 40 mg/dL	4 (14.3%)	0
Month 27		
TTR Level Category		
n	24	6
< 20 mg/dL	1 (4.2%)	3 (50.0%)
20 mg/dL – 40 mg/dL	21 (87.5%)	3 (50.0%)
> 40 mg/dL	2 (8.3%)	0
Month 30		
TTR Level Category		
n	24	7
< 20 mg/dL	1 (4.2%)	3 (42.9%)
20 mg/dL – 40 mg/dL	20 (83.3%)	3 (42.9%)
> 40 mg/dL	3 (12.5%)	1 (14.3%)

The sensitivity analyses showed consistent results and, therefore, demonstrated the robustness of the results of the TTR level. The results of the two supplementary analyses, conducted to address the potential effect of concomitant tafamidis initiated during the study, showed consistent results with the analysis of TTR level and TTR stabilisation measured in FPE and WB in the mITT Population. Adding tafamidis to acoramidis had no additional effect on TTR stabilisation (Table 7).

Table 14.2.1.53a
Summary and Change from Baseline in TTR Level Category by Visit and by Genotype
mITT Population

ATTRwt-CM		
	Acoramidis (N=370)	**Placebo (N=182)**
Month 21		
TTR Level Category		
n	265	142
< 20 mg/dL	11 (4.2%)	27 (19.0%)
20 mg/dL – 40 mg/dL	236 (89.1%)	113 (79.6%)
> 40 mg/dL	18 (6.8%)	2 (1.4%)
Month 24		
TTR Level Category		
n	270	132
< 20 mg/dL	5 (1.9%)	18 (13.6%)
20 mg/dL – 40 mg/dL	244 (90.4%)	114 (86.4%)
> 40 mg/dL	21 (7.8%)	0
Month 27		
TTR Level Category		
n	257	122
< 20 mg/dL	6 (2.3%)	16 (13.1%)
20 mg/dL – 40 mg/dL	218 (84.8%)	104 (85.2%)
> 40 mg/dL	33 (12.8%)	2 (1.6%)
Month 30		
TTR Level Category		
n	260	128
< 20 mg/dL	7 (2.7%)	16 (12.5%)
20 mg/dL – 40 mg/dL	227 (87.3%)	109 (85.2%)
> 40 mg/dL	26 (10.0%)	3 (2.3%)

Table 7: Summary of TTR stabilisation (%) Measured in FPE and WB at Month 30 and by Concomitant Tafamidis Groups, mITT Population

	Acoramidis Only (N = 348)	Placebo Only (N = 156)	Acoramidis+ Tafamidis (N = 61)	Placebo+ Tafamidis (N = 46)
TTR Stabilization (%) Measured in FPE at Month 30				
n	71	20	10	9
Mean (SD)	99.667 (18.4093)	-47.039 (117.8914)[a]	100.357 (15.6019)	47.302 (33.9622)
Median (Q1, Q3)	98.074 (93.540, 104.286)	-11.600 (-49.299, 13.221)	96.229 (91.003, 111.552)	48.890 (43.416, 65.907)
Min, Max	29.72, 194.49	-455.67, 70.79[a]	77.07, 131.33	-28.13, 87.84
FPE Category at Month 30				
≥ 75%	69 (97.2%)	0	10 (100.0%)	1 (11.1%)
≥ 90%	57 (80.3%)	0	8 (80.0%)	0
≥ 99%	33 (46.5%)	0	4 (40.0%)	0
Number of participants maintained ≥ 90% at both Day 28 and Month 30	46/67 (68.7%)	0	3/7 (42.9%)	0
TTR Stabilization (%) Measured in WB at Month 30				
n	82	24	13	13
Mean (SD)	89.722 (12.5239)	30.698 (15.2001)	81.296 (14.9883)	56.832 (19.3441)
Median (Q1, Q3)	87.359 (80.292, 95.547)	27.029 (19.724, 31.128)	84.690 (76.018, 91.093)	55.487 (41.800, 69.482)
Min, Max	64.23, 129.95	16.45, 73.07	43.15, 98.98	27.58, 98.61
WB Category at Month 30				
≥ 75%	78 (95.1%)	0	10 (76.9%)	1 (7.7%)
≥ 90%	37 (45.1%)	0	5 (38.5%)	1 (7.7%)
≥ 99%	16 (19.5%)	0	0	0
Number of participants maintained ≥ 90% at both Day 28 and Month 30	22/74 (29.7%)	0	2/10 (20.0%)	0

Abbreviations: FPE = fluorescent probe exclusion; Max = maximum; Min = minimum; mITT = modified intent-to-treat; Q = quartile; SD = standard deviation; TTR = transthyretin; WB = Western blot

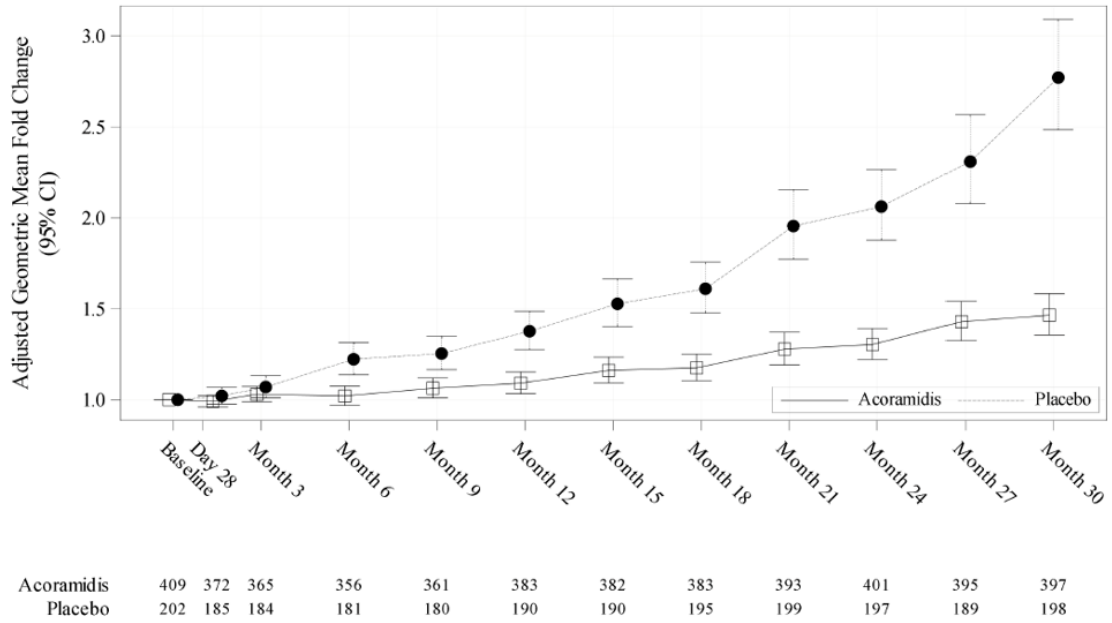
[a] Possible explanation for the negative value: FPE % stabilization relied on the Day 1 (baseline) sample for all calculations. If the baseline sample was weak or atypical, all other visits were impacted. If a later sample had a higher fluorescence than baseline, then % stabilization was negative.

Source: AG10-301 CSR, Table 14.2.1.98a and Table 14.2.1.102a

Regarding pharmacodynamic markers for myocardial effect of acoramidis, the levels of NT-proBNP and Troponin I were evaluated in study AG10-301 throughout the 30 months of study.

Figure 7 shows that the progressive rise in NT-proBNP observed over 30 months for placebo was nearly halved in the acoramidis treatment group. At month 30, a statistically significant treatment effect on NT-proBNP was observed favouring acoramidis, with the adjusted geometric mean fold change from baseline reduced from 2.77 for placebo to 1.47 for acoramidis. For NT-proBNP, the ratio of the adjusted geometric mean fold change from baseline to month 30 was 0.529 (95% CI: 0.463, 0.604; nominal p < 0.0001).

Figure 7: Adjusted Geometric Mean Fold-change (95% CI) from Baseline in NT-proBNP Over Time (with J2R), mITT Population



Acoramidis	409	372	365	356	361	383	382	383	393	401	395	397
Placebo	202	185	184	181	180	190	190	195	199	197	189	198

Abbreviations: CI = confidence interval; J2R = Jump to Reference; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
Source: AG10-301 CSR, Figure 14.2.1.69

The results of the supplementary analyses, conducted to address the potential effect of concomitant tafamidis, showed consistent results with the primary analysis of change from baseline in NT proBNP. Adding tafamidis to acoramidis did not lead to a greater decrease in NT-proBNP, as compared to acoramidis only.

In a post-hoc analysis with imputation that accounted for missing observations, at month 30, a net decrease in NT-proBNP relative to baseline, an indication of clinical improvement, was observed in 31.1% of participants in the acoramidis treatment group, compared to 5.9% in the placebo group ($p < 0.0001$).
At baseline, the mean high-sensitivity TnI was lower in the acoramidis treatment group (98 ng/L, n = 39) compared to placebo (204 ng/L, n = 15). At all timepoints, the percent change from baseline in high-sensitivity TnI was lower in the acoramidis treatment group compared to placebo. At month 30, a slight decrease in mean percent change from baseline in high-sensitivity TnI was observed in the acoramidis treatment group (mean: -2.08%), whereas an increase was observed in the placebo group (mean: 39.56%). None of these participants received tafamidis in the study.

Secondary pharmacology

Acoramidis was assessed *in vitro* and *in vivo* for cardiovascular safety. The human ether-à-go-go-related gene (hERG) ion channel activity was not significantly inhibited at concentrations up to 100 µM (safety panel). Non-GLP hERG patch clamp assay did not reach half maximal response in current inhibition (12.9% inhibition at 100 µM). GLP hERG patch clamp assay did not reach half maximal response in hERG current inhibition (3.2% inhibition at 10 µM and 2.1% inhibition at 50 µM). The reported IC50 of > 50 µM represents a > 33-fold margin over the free fraction of the high clinical exposure estimated at 12,300 ng/mL, the upper bound of the 95% CI for the day 28, 1-hour postdose concentrations observed in the PK/PD sub-study of AG10-301. A dog telemetry study demonstrated no concentration QT effect under GLP conditions established at multiple plasma concentrations above the

high clinical exposure estimated at 12,300 ng/mL, the upper bound of the 95% CI for the day 28, 1 hour postdose concentrations observed in the PK/PD sub-study of AG10-301 (48.2-fold margin).

On study AG10-001 safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and adverse events (AEs).

Part A consisted of a SAD design, where 4 cohorts of 8 healthy men and/or women were randomised to AG10 or matching placebo in a 3:1 overall ratio, with 1:1 sentinel dosing and subsequent 5:1 randomisation. The starting dose of AG10 was 50 mg. Tentative dose levels were 50, 150, 300, 600, 1200, and 2000 mg, but actual increases were based on a review of the safety and PK data of previous cohorts. The actual doses of AG10 were 50, 150, 300, and 800 mg. Subjects in Cohort 3 (300 mg AG10) were administered AG10 twice in a fixed-sequence crossover fashion: subjects were administered the drug product under fasted conditions in Period 1 and under fed conditions in Period 2.

Continuous 12-lead 24-hour Holter monitoring was initiated on day 1 and continued through 24 hours after dosing on day 1 (except in the second period of the food-effect cohort).

Part B consisted of a MAD design where 3 cohorts of 8 healthy men and/or women were randomised to AG10 or its placebo in a 3:1 ratio. This part was initiated after satisfactory review of safety data from at least 3 cohorts of healthy subjects in Part A. The doses for Part B were 100, 300, and 800 mg twice daily (BID).

Continuous 12-lead, 24-hour Holter monitoring was initiated on day 1 and continued for 24 hours after the first dose on day 1; on the last day of study drug administration, Holter monitoring was initiated prior to dosing and continued for 24 hours after the last dose.

All mean safety ECG parameters (heart rate, PR, QRS, QT, and QTcF) remained within normal limits at the assessed time points, with minimal changes from baseline observed that were not considered clinically significant.

Continuous 12-lead ECG Holter monitoring was performed for both the SAD and MAD cohorts in this study, with the average of triplicates used for summarisation.

Study AG10-005 was a Phase 1 Randomized, Placebo-controlled, Single Ascending Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Supratherapeutic Doses of AG10 in Healthy Subjects.

One of the secondary objectives was to describe the PK-PD relationship to measures of cardiac conduction and repolarisation, and of TTR stabilisation, of single, supratherapeutic oral doses of AG10 in healthy adult subjects.

In this single ascending dose (SAD) design, 3 cohorts of 9 healthy men and/or women were randomised to AG10 or matching placebo in a 2:1 overall ratio, with 1:1 sentinel dosing on

day 1 and subsequent 5:2 randomisation of the remainder of the cohort on the following day. The starting dose of AG10 was 1200 mg, with dose escalations to 1600 and 2000 mg, in separate cohorts, respectively. All available safety data from up to 72 hours following dosing at previous dose levels were reviewed prior to each dose escalation.

All mean safety 12-lead ECG parameters remained within normal limits at the postdose time points with minimal changes from baseline observed. A total of 4 subjects exhibited prolonged QTcF intervals > 450 msec and/or > 30 msec over the baseline value as follows:

- Subject (1200 mg AG10 [Cohort 1]) exhibited a QTcF interval of 435 msec on day 20, an increase of +31 msec above the baseline value of 404 msec.

- Subject (placebo) exhibited a QTcF interval of 419 msec on day 4, an increase of +33 msec above the baseline value of 386 msec.
- Subject (placebo) exhibited a QTcF interval of 458 msec on day 1 hour 4. The subject's baseline QTcF interval value was 439 msec.
- Subject (2000 mg AG10 [Cohort 3]) exhibited a QTcF interval of 459 msec on day 1 hour 4. The subject's baseline QTcF interval value was 450 msec.

Continuous 12-lead 24-hour Holter monitoring was initiated on day 1 and continued through at least 24 hours after dosing on day 2, with cardiodynamic Holter extractions transmitted to the core lab for subsequent analysis.

There were no ECG-related AEs during this study. The PI considered all individual out-of-range ECG results to be not clinically significant.

Retinol binding protein is the carrier for Vitamin A in plasma. Vitamin A deficiency is known to be associated with night blindness. In study AG10-301, the decreases in measured serum RBP in the acoramidis group were not accompanied by any clinical evidence of TEAEs that would be associated with Vitamin A deficiency over 30 months. There were no reports of night blindness TEAEs throughout the study. The incidence of vision AEs was comparable between the treatment groups: vison blurred (acoramidis: 1.0%; placebo: 0.5%) and visual impairment (acoramidis: 0.5%; placebo: 0.5%). There was one SAE of macular hole in the acoramidis group assessed as not related to study drug, instead related to pre-existing retinal hole. Acoramidis was continued and the event resolved. There were no TEAEs of clinical concern regarding vision changes.

In study AG10-301, mean TSH was comparable at baseline in both groups and remained stable in both groups throughout the dosing period at each time point. A higher percentage of participants with shift from normal to abnormal worst postbaseline values was observed in the acoramidis treatment group compared to the placebo group for serum free T4 (8.2% versus 3.8%), and from normal to abnormal last postbaseline values was observed in the acoramidis group compared to the placebo group (3.6% versus 1.9%; Section 12.3.2.2). There was no clinically meaningful difference in change from baseline of free T4, with a mean free T4 of 13.53 pmol/L at baseline, lowest mean was 11.96 pmol/L at month 6, and 12.28 pmol/L at month 30 in the acoramidis treatment group. There was no clinically meaningful difference in incidence of thyroid AEs, with hypothyroidism reported for 3.6% of participants in the acoramidis treatment group and for 2.8% in the placebo group. There was one SAE of hypothyroidism in the acoramidis group reported by the Investigator as not related to study drug, instead related to the participant's history of subclinical hypothyroidism and amiodarone administration, with elevated thyroid peroxidase antibodies and development of Hashimoto's thyroiditis. The Sponsor agreed the hypothyroidism was not related to acoramidis. No clinically meaningful impact on thyroid function was observed in either treatment group. Review of reported TEAEs (non-serious and serious) did not identify a clinically meaningful imbalance in thyroid events.

Secondary pharmacology non-clinical *in vitro* tests showed a lack of cytotoxic or antiproliferative effect of acoramidis on four mammalian cell lines (Hep3B, Jurkat, MCF3, Hela).

Off-target activity was not detected when acoramidis at a concentration of 100 µM was tested in the Panlabs/Eurofin panel of receptors, enzymes and ion channels. In contrast to known TTR ligands and cyclooxygenase (COX) inhibitors such as diflunisal, acoramidis does not inhibit COX enzymes or bind to thyroid hormone nuclear receptor at the tested concentration, thus no off-target activity is anticipated against these proteins.

2.6.3. Discussion on clinical pharmacology

Methods

Documentation and validation of the analytical methods is considered complete and acceptable.

Pharmacokinetics

Absorption

Generally, results from pharmacokinetic studies AG10-001, AG10-005, AG10-007 and AG10-003 indicate a consistency on acoramidis tmax across the all the dose levels tested, as single and multiple dose administration of acoramidis. Moreover, there was also comparable exposure (AUCs and Cmax) across the studies.

Following oral administration of single ascending doses of acoramidis (50, 150, 300 and 800 mg), there was a rapid absorption of the drug, with median plasma tmax values ranging from 0.75 to 1 hour across dose levels. Tmax individual values ranged from 0.5 to 3.0 hours across the four dose levels. Following oral administration of multiple ascending doses of acoramidis (100, 300 and 800 mg), the drug also showed a rapid absorption, with median plasma tmax values ranging from 0.75 to 1.1 hour across the three dose levels for multiple dose day 1 and ranging from 0.5 to 1.0 hour for multiple dose day 12 (steady state condition). Steady state for acoramidis was reached by day 10.

Following oral administration of single ascending doses of acoramidis (50, 150, 300 and 800 mg), exposure parameters (AUC0-t, AUC0-inf, and Cmax) for plasma acoramidis were lower than dose proportional (factor increases in dose of 1:3:6:16 produced increases of approximately 1:1.7:2:4.3 in AUC0-t and AUC0-inf, and 1:1.6:2.1:5.2 in Cmax). Following oral administration of multiple ascending doses of acoramidis (100, 300 and 800 mg) resulted in 1.3 to 1.6-fold accumulation of the compound based on the mean accumulation ratios for plasma acoramidis Cmax at steady state (day 12) and that on day 1 of dosing. Inter-individual variability was low, with a geometric %CV of 21.2% for AUCtau at steady state with 800 mg acoramidis HCl q12h dosing for 12 days.

Following oral administration of supratherapeutic single ascending doses of acoramidis (1200, 1600 and 2000 mg), there was a rapid absorption, with a median plasma tmax value of 1 hour across dose levels. Tmax individual values ranged from 0.5 to 2.0 hours across the three dose levels. A saturation of exposure was observed at doses between 800 mg and 1200 mg acoramidis HCl.

Based on results from mass balance study, acoramidis was also rapidly absorbed following a single dose administration (~450 µCi) [14C]-acoramidis), with a median plasma tmax value of 0.75 hours. Tmax individual values ranged from 0.5 to 1.0 hours. Considering results from total radioactivity in urine, it is expected that at least 68% of a single 800 mg acoramidis dose is absorbed. The applicant has added the following wording into SmPC section 5.2 (Absorption):

"The absolute bioavailability is not known; however at least 75-80% of orally administered single 712 mg dose is absorbed based on a human ADME (absorption, distribution, metabolism, excretion) study."

The proposed sentence is agreed.

Based on results from bioequivalence study, there was a rapid acoramidis absorption following a single dose administration (as 1 x 400 mg and 2 x 200 mg as acoramidis HCl), with a median plasma tmax value of 0.75 hours. Tmax individual values ranged from 0.5 to 3.0 hours.

Based on caco-2 *in vitro* assays, acoramidis was identified as an efflux substrate.

In vitro studies using MDCK-II cells treated to express BCRP indicated that acoramidis is a substrate for BCRP, but with no indication of saturation at concentrations up to 100 µM. *In vitro* studies using

MDCK MDR1 cells indicated that acoramidis is not a clinically relevant substrate as defined by the FDA (FDA, 2020) and EMA Guidance (EMA, 2012) for human P-gp and that it does not inhibit P-gp.

Acoramidis is an amphoteric compound, with pKa values of ~4.16 (pyrazole) and ~4.13 (carboxylic acid). The solubility of acoramidis HCl is pH dependent with a solubility of 5.63 mg/mL at a pH of 1.2 and 1.14 mg/mL at a pH of 6.8. The 712 mg dose is not completely soluble in ≤ 250 mL of aqueous media over the physiologically relevant pH range of 1.2 to 6.8, and thus acoramidis is classified as a low solubility compound based on the International Council for Harmonisation M9 BCS criteria. According to the applicant, the permeability classification for acoramidis in the BCS system has not been established due to efflux observed in permeability assays. In the Caco-2 permeability assay, the permeability results for acoramidis in the A→B direction for concentrations of 1, 10, and 50 µM were 0.04 ± 0.01 x 10-6 cm/s, 0.04 ± 0.00 x 10-6 cm/s, and 0.07 ± 0.01 x 10-6 cm/s, respectively. The efflux ratios were 421, 347, and 181 for concentrations of 1, 10, and 50 µM, respectively. The applicant has concluded that because passive transport is required to establish the BCS permeability classification using the Caco-2 assay, there are no data available to definitively assign a BCS permeability classification.

However, and according to ICH M9 Guideline, permeability may be estimated based on results from mass balance study using urine recovery data as the sum of parent drug (unchanged), Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in faeces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in faeces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in faeces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.

The proposed wording for section 5.2 of the SmPC regarding “Absorption” is supported by data and agreed.

Bioavailability

The absolute bioavailability of acoramidis has not been assessed in humans. The applicant has added the following wording into SmPC section 5.2 (Absorption):

“The absolute bioavailability is not known; however at least 75-80% of orally administered single 712 mg dose is absorbed based on a human ADME (absorption, distribution, metabolism, excretion) study.”

The proposed sentence is agreed.

In mouse, rat, dog, and monkey, absolute oral bioavailability values were found to be 30.5%, 59.7%, 39.5%, and 49.4%, respectively.

Food Effect

Characterisation of the influence of food on acoramidis absorption following oral administration is based on data from studies AG10-001 and ALXN2060-HV-101. Study AG10-001 was performed with the preliminary formulation and the power of this study with n = 6 is considered limited. Hence for conclusion it is focused on study ALXN2060-HV-101.

In study ALXN2060-HV-101, following a single dose of 800 mg acoramidis HCl, the extent of exposure (AUC) to acoramidis was comparable in the presence of a high-fat, high-calorie meal and under fasted conditions (i.e. the differences in AUC are within the common acceptance limits for bioequivalence [80.00 – 125.00]%). However, a decrease in Cmax and a delay in Tmax were noted. Nevertheless,

and considering the Cmax at steady state (12,400 ng/mL), the difference in Cmax observed between the two formulations (fasted 8,988 ng/mL vs fed 7,020 ng/mL) is assumed to be of limited clinical relevance. Given that this decrease in peak exposure is considered as not clinically significant, administration of acoramidis with or without food is supported.

In phase III study (AG10-301), participants were instructed to self-administer acoramidis BID, once in the morning and once in the evening, with or without food. Such recommendations were in line with results from food effect studies.

The proposed wording for section 5.2 (Absorption) of the SmPC, stating that the overall extent of absorption of acoramidis is not influenced by food intake, is supported by data and agreed.

Bioequivalence

Bioequivalence was demonstrated between the new 'high strength' acoramidis HCl 400 mg tablet formulation of acoramidis (Test) for Phase 3 studies and the original tablet formulation acoramidis HCl 200 mg (Reference) in terms of the extent of acoramidis absorption but not in terms of the rate of acoramidis absorption. Nevertheless, considering the Cmax at steady state (12,400 ng/mL with a CV of 54 %) and the difficulty to determine the very pointed Cmax correctly, the difference in Cmax observed between the two formulations (4,190 ng/mL for the 400 mg tablet formulation vs 5,330 ng/mL for the original 200 mg tablet) is assumed to be of limited clinical relevance. Comparison of PK-data from the studies AG10-201 and AG10-301 did not indicate a substantial difference. Hence the results gained with the 200 mg formulation are considered acceptable in this marketing authorisation application.

Distribution

The method used to investigate the extent of acoramidis protein binding in plasma from Sprague Dawley rats, beagle dogs, cynomolgus monkeys, and humans is adequate and properly validated. Generally, a high protein binding was found across all species. Tested concentrations of 10 µM and 50 µM corresponds to 2923 ng/mL and 14616 ng/mL, respectively (MW of acoramidis is 292.31 g/mol). These concentrations are similar to acoramidis plasma concentrations Cmin (2450 ng/mL) and Cmax (12400 ng/mL) estimated for steady state following multiple oral dose administration (BID) of acoramidis HCl 800 mg in study AG10-001 (Table 4), which is the recommended posology.

No binding to erythrocytes is expected based on *in vitro* results. Tested concentrations of 0.1 µM (29.2 ng/mL) to 10 µM (2923 ng/mL) cover the expected range of free plasma concentrations of acoramidis in steady state following multiple oral dose administration (BID) of acoramidis HCl 800 mg (i.e., 88 ng/mL to 446 ng/mL based on Cmin and Cmax and assuming an unbound fraction of 3.6%).

The proposed wording for section 5.2 of the SmPC regarding "Distribution" is supported by data and agreed.

Elimination

In the mass balance study AG10-007, a total dose of 800 mg (~450 µCi) [14C]-acoramidis HCl on the form of oral suspension was administered. A dose level of 800 mg acoramidis HCl was selected for this study once it was expected to provide a well-characterised PK profile at a safe and well-tolerated dose. Moreover, the administered 800 mg dose corresponds to the recommended oral dose (BID) for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). No issues related to a decrease on the oral bioavailability are expected following administration on the form of suspension in comparison to tablets.

A total of 102% of total radioactivity was recovered (urine and faeces).

Based on results from mass balance study AG10-007, after a single dose of 800 mg (~450 µCi) [14C]-acoramidis HCl oral suspension, approximately 34% of the dose was recovered in faeces (approximately half as unchanged drug and half as metabolites), and approximately 68% of the dose was recovered in the urine. Based on urinary concentrations, the percent of unchanged acoramidis in the urine was approximately 8% and the percent of acoramidis-AG metabolite was 31%. Based on radioactivity metabolite profiling, the percent of unchanged acoramidis in the urine was approximately 10% and the percent of acoramidis-AG metabolite was 37%. Results are concordant.

Results from SAD/MAD study AG10-001 indicate an increase of Cl/F, V/F and Clr with increasing dose, following both single and multiple dose administration. However, no increase on the elimination half-life was observed, with a general mean of approximately 27 h following multiple dose administration. Increase of Cl/F and V/F may be due to a decrease in the bioavailability (F) of acoramidis. The applicant has justified the potential decrease in the bioavailability (F) of acoramidis with increasing dose, due to acoramidis low solubility. However, no reason was found for the increase of renal clearance with increasing dose. Nevertheless, the applicant justifies that such increase has no clinical relevance, given that < 10% of unchanged acoramidis is excreted renally. This is agreed.

Conspicuous is also the very high and early Cmax followed by fast decrease of the plasma concentration. This is exemplified e.g. in study AG10-001, on which, following multiple dose administrations of 800 mg acoramidis, the acoramidis plasma concentration on day 12, after 1 h post dose, showed a mean of 13600 ng/ml, followed by 4670 ng/ml one hour later (2 h post dose sample). If Ctrough is subtracted, this drop is even more prominent (10920 ng/ml to 1990 ng/ml). Therefore, it is observed that more than 80 % of the acoramidis dose response is reduced from plasma within one hour. A coherence with renal excretion might be suspected, as 40 % of total radioactivity is detected in the urine collected in the first 4 hours after dosing. This finding is not discussed and the responsible mechanisms for metabolism (the amount of unchanged acoramidis in the urine is < 10%) and excretion are not clear.

The metabolic pathway was considered, at least in part, not fully clear. The applicant mentioned a redistribution “from the plasma to the target compartment”. However, it was not clear what constitutes this target compartment. As transthyretin is a protein in the plasma, the plasma is considered the target compartment.

It is further suggested that acoramidis is rapidly metabolised to acoramidis-AG. Multiple UGT enzymes catalyse acoramidis-AG formation, probably in the liver. Estimates of the relative contribution of the UGTs to the *in vitro* formation of acoramidis-AG suggested that the major contribution appeared to be from UGT2B7 (53.1%), followed by UGT1A9 (28.2%) and UGT1A1 (13.3%). It is acknowledged that in healthy subjects the acoramidis-AG PK is comparable to that of the parent compound.

Though this might be no speed-limiting process in healthy subjects, this is less clear in the case of hepatic impairment. This issue needs thorough investigation. Furthermore, it was substantiated that inhibition of certain UGT-enzymes, in particular UGT2B7 and UGT1A9, does not relevantly reduce acoramidis-AG formation and delay decline of acoramidis plasma concentration. It was reminded, that ~ 80 % of the acoramidis increase in plasma concentration after dosing disappear from the plasma within 2 h, probably mostly by glucuronidation to acoramidis-AG.

These uncertainties hold true for acoramidis-AG PK. In healthy subjects, it is assumed, that acoramidis-AG is eliminated by renal filtration. However, in this case, renal function becomes a pivotal factor. Besides pharmacological activity of acoramidis-AG itself, glucuronidation of acoramidis might be inhibited by accumulation of acoramidis-AG (product inhibition). The applicant has clarified all the above issues.

The proposed wording for section 5.2 of the SmPC regarding “Elimination and Excretion” is supported by data and agreed.

Biotransformation

Based on *in vitro* metabolic assays with human liver microsomes and human hepatocytes, a minimal CYP-enzyme involvement in the metabolism of acoramidis is expected. The major metabolic pathway was acyl glucuronidation, leading to the formation acoramidis-AG.

Acoramidis-AG accounts for only 30.8% of total radioactivity of human urine and its formation *in vivo* is presumably catalysed by multiple UGTs as suggested by in vitro studies. As indicated in the above table, the in vivo contribution of UGT2B7, UGT1A9 and UGT1A1 is 16.3, 8.7, and 4.1%, respectively. Nevertheless, this metabolite represents only a mean of 6.5% of the circulating total radioactivity (based on AUC0-inf) and is 3-fold less pharmacologically active than acoramidis. Acoramidis-AG has a low potential for covalent binding and therefore does not meaningfully contribute to the pharmacological activity. The remaining metabolites in plasma accounted for < 6% each of the circulating total radioactivity.

The proposed wording for section 5.2 of the SmPC regarding "Biotransformation" is generally supported by data and agreed. However, it is stated that *"Acoramidis is metabolised predominantly by glucuronidation, with acoramidis-β-D-glucuronide (acoramidis acylglucuronide, acoramidis-AG) being the predominant metabolite (7.64% of total circulating radioactivity)."* It seems that a percentage of 7.64% was derived as the mean of the ratio PE (AUC0-96h) acoramidis-AG by AUC0-96h, total radioactivity, i.e. the calculation is referred to AUC0-96h and not to AUC0-inf. According to assessor calculations based on AUC0-inf, the mean percentage is estimated as 6.5%. The applicant has justified the use of AUC0-t for the calculation of the ratio AUC0-96h, acoramidis-AG by AUC0-96h, total radioactivity as per SAP description. The applicant has also determined this ratio based on AUC0-inf, concluding that acoramidis-AG represents 6.56% of total circulating radioactivity. Such estimate is proposed to be included in SmPC section 5.2 (Biotransformation) as below:

"*The metabolism of acoramidis was characterised following the administration of a single oral dose of [14C]-acoramidis to healthy adult volunteers. Acoramidis is metabolised predominantly by glucuronidation, with acoramidis-β-D-glucuronide (acoramidis-AG) being the predominant metabolite (6.56% of total circulating radioactivity)."* The proposed sentence is agreed.

In the mass balance study, acoramidis-AG represented only 6.5% of total circulating radioactivity. Moreover, acoramidis-AG has a low potential for covalent binding and therefore does not meaningfully contribute to the pharmacological activity. Nevertheless, the pharmacokinetics of acoramidis-AG was evaluated in study AG10-001 following SAD and MAD of acoramidis HCl and no concerns are raised based on study results.

Dose proportionality and time dependency

Following single ascending dose administration of acoramidis HCl, a non-linear relationship with dose was observed for acoramidis AUC0-inf and Cmax. For AUC0-t, a linear but non-proportional (less than proportional) relationship with dose was observed.

Following q12h doses of acoramidis HCl for 12 days, a non-proportional (less than proportional) relationship with dose was concluded for plasma acoramidis PK parameters AUC0-t, AUC0-inf, and Cmax following multiple oral doses of acoramidis HCl in the 100 to 800 mg range. The applicant has justified the non-linearity observed for Cmax and AUC0-inf following single ascending doses of acoramidis HCl in the range of 50 mg to 800 mg due to the low solubility of the compound, and consequently a solubility-limited absorption. This justification is acceptable.

Time dependency was not evaluated in study AG10-001 (Part B – MAD). Nevertheless, considering data from the Part A (SAD) and from Part B (MAD), it is possible to approximately estimate the

stationary ratio as ⟦AUC⟧_(0-τ,SS)/⟦AUC⟧_(0-inf,SD) . A stationary ratio of 0.38 is estimated for the 800 mg acoramidis HCl dose, which indicates a time-dependency issue.

Following 800 mg acoramidis HCl multiple doses BID, the mean accumulation ratio for plasma acoramidis Cmax and AUC0-(was 1.3, which is less than the estimated accumulation ratio of 3.8 based on the elimination half-life found following the single dose administration of acoramidis HCl 800 mg (i.e. 27.5h).

The applicant has addressed adequately the issues related to time-dependency considering the estimated stationary ratio of 0.38 (determined as ⟦AUC⟧_(0-τ,SS)/⟦AUC⟧_(0-inf,SD)), and the accumulation of acoramidis in a BID regimen. According to the applicant, a PBPK model suggested a delayed absorption in colon, which may originate a flip-flop kinetics, biasing the observed elimination t1/2 of acoramidis. The applicant has estimated an effective elimination t1/2 as 8.5h.

The applicant describes in SmPC section 5.2 (Elimination and excretion) that *"the terminal half-life of acoramidis is approximately 27 hours after a single dose"*. This sentence is agreed as being in line with the applicant's justification.

Intra and inter-individual variability

The intra and inter-individual variability was adequately addressed by the applicant based on popPK modelling results. Inter-individual variabilities for disposition parameters are moderate (38-55%) and considering a very fast absorption (absorption half-life of 0.069 hours), inter-individual variability for absorption has no relevance. A slightly higher intra-individual error was estimated for patients in comparison to healthy subjects, as expected. A sentence indicating intra - individual variability is included in the SmPC, which is acceptable.

Pharmacokinetics in the target population

Health status was selected as a covariate in the final population PK model, affecting acoramidis CL/F and Vc/F model parameters. A sensitivity analysis showed that healthy subjects had a 37% higher acoramidis exposure than ATTR-CM patients and that Vc/F was 144% higher in healthy subjects, reducing their maximum concentration (Cmax). However, this finding seems not to be in accordance with the pcVPCs depicted for healthy volunteers and patients, where exposure in patients appears to be higher than in healthy subjects. The applicant has clarified that the population PK model predicted a lower apparent clearance (CL/F) in healthy subjects in comparison to that in patients, resulting in 37% higher acoramidis exposure. This is observed in the prediction-corrected VPC for normalised concentration plots and in the individual predictions (IPREDs) normalised by dose multiplied by bioavailability plot. Moreover, the applicant has included in SmPC section 5.2 (Special populations) the following sentence, which is agreed:

"Based on population PK modelling, steady-state acoramidis AUC was 37% higher for healthy subjects than for the patient population. Also, relative to White subjects, steady-state AUC was 23% higher for Black subjects and 38% higher for non-White, non-Black subjects. These effects are within the range of inter-individual variability (CV = 38%). (…)"

Moreover, the plasma levels of acoramidis acylglucuronide are consistently higher in patients. It is assumed that in patients acoramidis acylglucuronide AUC is considerably higher than the AUC of acoramidis, and that the decline in plasma concentration from 1 h to 2 h post dose is lower in comparison to acoramidis (e.g., in study AG10-201, on which, following multiple dose administrations (BID) of 800 mg acoramidis into patients, the acoramidis acylglucuronide plasma concentration on steady state, after 1 h post dose, showed a mean of 17064 ng/ml, followed by 13877 ng/ml one hour later (2 h post dose sample). Hence, a noticeable contribution of acoramidis acylglucuronide to PD, efficacy and safety is expected. Based on the totality of these data, the applicant does not anticipate

any clinically significant issues arising from a hepatic or renal insufficiency or DDI perspective of acoramidis-AG. The applicant has argued that acoramidis-AG only represents 7.6% of the circulating total radioactivity (based on AUC), based on results of the human ADME study (AG10-007). Moreover, once acoramidis-AG metabolite has only 24% to 34% activity of that of parent acoramidis, it is expected that its contribution to overall pharmacological activity cannot exceed 4%, which may be considered as negligible. In summary, the applicant concluded that a potential accumulation of acoramidis-AG due to renal impairment is not expected to impact clinical efficacy or safety.

Nevertheless, and despite the above may be acceptable for mild and moderate decreased renal function (GFR > 30 ml/min), the consequences on the accumulation of acoramidis-AG in severe renal impairment, especially on high daily dose, cannot be disclosed. Therefore, the applicant included in section 5.2 (Special populations) a sentence addressing the potential impact of renal impairment in the pharmacokinetics of acoramidis.

Based on results from pre-clinical and clinical studies, the applicant has concluded that acoramidis has a wide therapeutic window based on the proposed posology of acoramidis 712 mg (two tablets, 356 mg) (800 mg acoramidis HCl) orally, twice daily. This conclusion is agreed.

Specific populations

Renal impairment

The applicant has adequately justified why a dedicated pharmacokinetic study in subjects with decreased renal function was not performed. Justification is in line with *EMA Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014)*. Moreover, in the population modelling, which included data from patients enrolled in phase 2 and/or phase 3 studies with decreased renal function (Cl_{CR} values from 25.4 to 89 mL/min, corresponding from severe to mild renal impairment patients), the final popPK model did not include renal function as a covariate. Therefore, popPK model found no significant differences in the pharmacokinetics of acoramidis based on renal function.

The lack of data from a dedicated pharmacokinetic study in subjects with decreased renal function is reflected in the SmPC in section 5.2 (Specific Populations) as below:

"Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis. Clearance of the acoramidis metabolite acoramidis-AG might be affected by severe renal impairment. Hence acoramidis should be used with caution in patients with severe renal impairment."

Moreover, the impact of severe renal impairment on the accumulation of plasma acoramidis-AG and consequently on the potential inhibition of acoramidis glucuronidation and overall pharmacological activity is addressed in section 5.2 (Special populations) of SmPC, as below:

"A dedicated renal-impairment study was not conducted because acoramidis is not substantially eliminated by the renal route. However, despite the main metabolite (acoramidis-AG) having no clinically relevant contribution to pharmacological activity in the studied population, data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis. Clearance of the acoramidis metabolite acoramidis-AG might be affected by severe renal impairment resulting potentially in higher systemic exposure of acoramidis-AG. While this potential increase in acoramidis-AG exposure is not expected to have a clinically meaningful contribution to pharmacologic activity. Hence, acoramidis should be used with caution in patients with severe renal impairment."

Wording is agreed.

Hepatic impairment

The applicant has adequately justified why a dedicated pharmacokinetic study in subjects with impaired hepatic function was not performed. Justification is in line with *EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02).* Acoramidis is not intended to be used in patients with impaired hepatic function. The applicant has revised sections 4.2 and 4.4 of SmPC as below:

"Acoramidis has not been studied in patients with hepatic impairment and therefore is not recommended for use in this population (see sections 4.4 and 5.2)"

The applicant has also included in SmPC section 5.2 (Special populations) the following sentence:

"Acoramidis has not been studied in patients with hepatic impairment."

Gender

No clinically significant differences in the pharmacokinetics of acoramidis were observed based on gender, after testing this intrinsic factor in the popPK modelling. This finding is reflected in section 5.2 (Specific Populations) of the SmPC.

Ethnicity

Following single oral doses of acoramidis HCl, overall exposure to acoramidis, as measured by geometric mean AUC0-tlast, AUC0-inf, and Cmax was comparable between Japanese and non-Japanese participants for the 400 mg and 800 mg dose levels, with a proportionality factor of 1.0 to 1.2 between the 400 and the 800 mg dose levels.

Moreover, no clinically significant differences in the pharmacokinetics of acoramidis were observed based on race, after testing this intrinsic factor in the popPK modelling.

This finding is reflected in section 5.2 (Specific Populations) of the SmPC.

Body weight

No clinically significant differences in the pharmacokinetics of acoramidis were observed based on body weight, after testing this intrinsic factor in the popPK modelling. The applicant has included in SmPC section 5.2 (Special populations) the following sentence, which is agreed:

"(…). The model also predicted lack of clinically significant differences in the pharmacokinetics of acoramidis due to body weight, within the body weights range of 50.9 to 133 kg."

Age

The pharmacokinetics of acoramidis was studied in healthy subjects and in patients with sparce sampling (studies AG10-201, AG10-202, and AG10-301) for the quantification of pre-dose levels. Across all studies performed with patients, all participants were in the range of 57 to 89.3 years. The population PK modelling tested age as a covariate and no clinically significant differences in the pharmacokinetics of acoramidis were observed based on this intrinsic factor. This finding is reflected in section 5.2 (Specific Populations) of the SmPC, as well as in section 4.2 (Posology and method of administration) of the SmPC, where it is stated that *"No dose adjustment is required in elderly patients (≥ 65 years, see section 5.2)."*

Paediatric population

A product-specific waiver, covering ATTR-CM and ATTR-PN, as ATTR-CM does not occur in any paediatric subset and clinical studies are not feasible in ATTR-PN paediatrics patients due to isolated cases of children affected by this condition, was granted on 8 October 2018 (P/0330/2018).

According to section 4.1 (Therapeutic indications) of the SmPC, acoramidis is only indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

In vitro metabolism and transport assays

Both, *in vitro* metabolic stability assay of acoramidis with HLM and *in vitro* metabolite identification study of acoramidis in human hepatocytes indicated minimal CYP involvement in the metabolism of acoramidis. In human hepatocytes experiments, an acoramidis concentration of 10 µM was used, which is within the mean range of [0.302 to 1.527]µM found in study AG10-001 as Cmin,ss and Cmax,ss following multiple dose administration of 800 mg acoramidis HCl. The acoramidis concentration used in the experiment is therefore acceptable.

Moreover, a positive control, 7-ethoxycoumarin (7-EC) at 100 µM, was incubated concurrently to assess Phase I and Phase II metabolic activities, respectively, of hepatocytes, which is acceptable. Acoramidis was also shown to be chemically stable in hepatocyte incubation media after the 4-hr incubations.

In vitro assays also concluded that acoramidis-β-D-glucuronide was the predominant metabolite and that the major contribution to its formation appears to be from UGT2B7, followed by UGT1A9 and UGT1A1.

Nevertheless, given that acoramidis-AG accounts for only 30.8% of total radioactivity of human urine, it was estimated that none of the individual UGT isozymes contributes > 20% to acoramidis-AG formation *in vivo*. Therefore, a clinically relevant DDI is not expected for any of the single UGT enzymes involved in catalysis of the acoramidis-AG pathway. Furthermore, only 7.6% of the circulating TRA in plasma following administration of [14C]-acoramidis was associated with plasma acoramidis-AG AUC (Study AG10-007), which is one-third as active as the parent, thus a clinically relevant DDI is not expected for circulating acoramidis-AG.

Acoramidis was tested in the concentration range of 0.15 to 150 µM as inhibitor of human CYP450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and CYP2D6, and in the concentration range of 1.1 to 1100 µM as inhibitor of human CYP450 CYP3A4/5. The range of concentrations cover more than 50 times the mean unbound plasma Cmax,ss following multiple 800 mg acoramidis HCl dose (50*Cmax,ss, unbound = 76.36 µM) and also the potential intestinal concentration (973 µM) determined as the single dose of acoramidis (711 mg) divided by 250 mL (volume of the glass of water) for CYP3A4 evaluation.

Acoramidis did not significantly inhibit any of the seven major human CYP450 isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9, CYP2D6 [IC_{50} > 150 µM], and CYP3A4/5 [IC_{50} > 1100 µM]). However, acoramidis caused irreversible metabolism dependent inhibition of CYP2C8 and CYP2C9 (IC50 of 76 µM and 100 µM, respectively) after a 30 minutes preincubation with NADPH. The unbound steady state plasma concentrations following multiple dose administration of 800 mg q12h is 1.51 µM, which is 50-fold and 66-fold lower than the IC_{50} values for CYP2C8 and CYP2C9, respectively, corresponding to a predicted inhibition of approximately 4% of CYP2C8 and 6% of CYP2C9. Given that a dedicated DDI clinical study was not performed, the following sentence was included in section 4.5 of the SmPC until robust DDI data are available:

"Based on in vitro studies, acoramidis is unlikely to cause any clinically relevant uridine 5'-diphospho (UDP)-glucuronosyl transferase-dependent or Cytochrome P450-dependent interactions. However, acoramidis was shown to be a weak inhibitor of CYP2C8 and CYP2C9 in vitro. No in vivo study has been performed. Therefore, concomitant CYP2C8 and CYP2C9 substrates with narrow therapeutic index should be used with caution.".

In vitro assays have also concluded no evidence of inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A6, and UGT2B15 by acoramidis, in the concentration range of [0.2 – 200]µM and have concluded to inhibit UGT1A9 to a maximum of 35% (IC50 >150 µM) and UGT2B7 to a maximum of 21% (IC50 >200 µM). The range of acoramidis concentrations used in these experiments cover the range from unbound Cmin,ss (0.302 µM) to more than 50 times the mean unbound plasma Cmax,ss, following multiple 800 mg acoramidis HCl dose.

Acoramidis was shown to be not an inducer of CYP1A2, CYP2B6, and CYP3A4 in the acceptable concentration range of 0.15 to 150 µM. Additionally it is also estimated that induction of UGT2B7 and UGT1A9 by acoramidis is unlikely to cause any potential clinically relevant DDI, given the low contribution of these enzymes to acoramidis metabolism.

Regarding transporters, it was concluded that acoramidis is not a substrate for OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, or BSEP, but is a substrate for OAT1 and BCRP, in the acceptable concentration range of 0.3 to 30 µM. For OAT1, the Km value was determined to be 28.5 µM (corresponding to 8331 ng/mL) with a Vmax of 45.4 pmol/min/cm2, and for BCRP, the Km value was > 100 µM (corresponding to 29231 ng/mL), and the Vmax value could not be determined. According to the applicant, and given the high Km values and the relatively low amounts of intact acoramidis excreted in urine, no clinically significant DDIs are anticipated for acoramidis as a substrate of these transporters.

The applicant has justified the low risk of DDI with BCRP inhibitors based on the low intestinal solubility of acoramidis and on expected site of absorption (colon) which shows a low expression of BCRP transporters. The applicant has updated SmPC section 4.5 as below:

"Acoramidis is a substrate for breast cancer resistance protein (BCRP). Based on an in-vitro study, no drug-drug interaction with co-administered BCRP substrates (e.g., rosuvastatin, methotrexate, imatinib) or inhibitors is anticipated at clinically relevant concentrations."

No statistically significant inhibition of transport mediated by human OCT1, OCT2, OATP1B1, OATP1B3, MATE2-K, BSEP, P-gp, or BCRP was observed *in vitro* by acoramidis at a concentration of 30 µM. Therefore, no clinically relevant DDIs with substrates of these transporters are anticipated. However, acoramidis inhibited *in vitro* transport mediated by OAT1, OAT3, and MATE-1, with IC50 values estimated to be 1.39 µM, 1.26 µM, and 178 µM, respectively. Based on the calculated Imax,u/IC50 values, there may be a potential for clinical DDIs with OAT1/OAT3 substrates such as loop diuretics (e.g., furosemide) which are the most common co-medication class used to manage heart failure in patients with ATTR-CM.

Regarding the potential inhibition by acoramidis-AG, at a concentration of 20 µM no statistically significant inhibition was seen for OCT2 or MATE2-K mediated transport, but was seen for transport mediated by OAT1 (22.8%), OAT3 (63.5%), and MATE1 (32.3%). IC50 was then determined only for OAT1 (36.7 µM). All the in vitro experiments used as transporter substrates the ones defined by FDA at *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-1.*

The ICH guideline M12 on drug interaction studies uses IC50 and Ki more or less interchangeably, and states that the Ki of an inhibitor approaches IC50 when the substrate concentration is much less than Km (using the Cheng-Prusoff equation). For the transporter experiments conducted on acoramidis, all substrates were used at concentrations much below the Km value, so the IC50 values are close to the Ki values. In the PBPK model, OAT3 Ki values were incorporated into model assuming IC50 = Ki, based on the incubation conditions in the in vitro experiment (substrate concentration << Km). Sensitivity analysis simulations were performed using Ki = IC50/5, Ki = IC50/10, Ki = IC50/15, Ki = IC50/30 and

Ki = IC50/100 which showed that interaction level remained low (< 2-fold). The applicant has appropriately clarified the calculation of IC50 instead of Ki, assuming IC50 = Ki.

Given the potential inhibition effect of acoramidis and acoramidis-AG on OAT1 and OAT3, a clinical DDI study (AG10-008) was conducted in HAV to assess the potential inhibitory effect of acoramidis (and acoramidis-AG) on OAT1 and OAT3 substrates.

Following results from in vitro studies where a potential DDI was suggested by inhibition of human OAT1 (IC50 = 1.39 µM) and OAT3 (IC50 = 1.26 µM) by acoramidis, study AG10-008 was performed.

Drug-Drug Interactions

The dedicated DDI Study AG10-008 was appropriately designed. Potential maximum inhibition of transporters OAT1 and OAT3 was achieved through steady state acoramidis concentrations following the recommended posology of 800 mg BID during 8 days (Part 1) and 9 days (Part 2). Study report shows in plots that acoramidis steady state (through concentration) was achieved within these administration periods.

Adefovir and oseltamivir carboxylate are recommended by the FDA as substrates for clinical DDI studies of OAT1 and OAT3, respectively (FDA, 2020).

Study AG10-008 showed a minimal inhibitory effect on OAT1 and no inhibitory effects on OAT3 after oral administration of 800 mg acoramidis.HCl q12h for 8 or 9 consecutive days. Based on these results, it is agreed that no dose recommendations are needed for potential co-administration of acoramidis and OAT1 substrates.

The proposed wording for section 4.5 of the SmPC regarding “Interaction with other medicinal products and other forms of interaction” is supported by data and agreed.

Despite acoramidis has a marked pH dependent solubility in the physiological pH range, popPK model and a dedicated DDI study with omeprazole and pentagastrin conducted in dogs could suggest that proton pump inhibitors or gastric reducing agents do not have an impact on the circulating plasma levels of acoramidis. However, preclinical DDI studies are not normally considered sufficient to exclude a risk of clinical interaction and it is challenging to exclude interactions based on pop-PK data, especially when a very low number of patients included in the popPK analysis had taken proton pump inhibitors (PPIs). Moreover, and despite absence of food effect may provide some support, food increases gastric pH less than PPI treatment and also has other concomitant effects which may confound the assessment of the potential interaction.

Nonetheless the marked pH dependent solubility of acoramidis in the physiological pH range, a dedicated *in vivo* DDI study with gastric acid reducing agents was not performed. Therefore, the applicant has included the following sentence in section 4.5 (Effect of other medicinal products on acoramidis) of the SmPC:

“Effect of other medicinal products on acoramidis

No dedicated in vivo drug-drug interaction study with gastric acid reducing agents was performed. Thus, the effect of gastric acid reducing agents on the pharmacokinetics of acoramidis is unknown. Despite the marked pH dependent solubility of acoramidis in the physiological pH range, no differences were observed in the systemic exposure to acoramidis or in the pharmacodynamic marker (TTR stabilisation) between patients taking acid reducing agents and patients not taking acid reducing agents, in the phase 3 study.”

Exposure Relevant for Safety Evaluation

The exposure derived from post hoc popPK analysis for the ATTR-CM target population from all patients following a dose regimen of 800 mg BID was similar to the exposure derived for healthy subjects on the same regimen.

For patients with impaired renal function, no clinically significant increase in exposure to acoramidis is expected given that renal elimination is a minor pathway contributing to elimination of unchanged acoramidis.

No posology modifications are described in the SmPC.

Population Pharmacokinetic Analysis

A population PK model for acoramidis was developed using NONMEM, based on data from 121 healthy subjects in 5 Phase 1 studies and 185 subjects with symptomatic ATTR-CM in 3 Phase 2-3 studies. Acoramidis PK was well described by a 2-compartment disposition model with sequential zero-order and first-order absorption. Dose-dependent bioavailability and food effects on both absorption rate (Ka) and absorption duration (D1) parameters were included. The final model included the effects of health status (ATTR-CM patient or healthy) on apparent clearance (CL/F) and apparent central volume (Vc/F), and of race on CL/F. Other covariates tested, including age, baseline body weight, baseline creatinine clearance, baseline estimated glomerular filtration rate, sex, concomitant medication (diuretics), were not identified as statistically significant on clearance or central volume. Vc/F was higher in healthy subjects, reducing Cmax without affecting AUC. CL/F was lower (i.e., AUC was higher) in healthy subjects, in Black patients, and in non-White, non-Black patients. However, these effects were within the range of variability due to residual error, so they were not thought to be clinically relevant.

Univariate covariate analysis showed age as a strong covariate affecting both CL/F and Vc/F. However, health status (patient or healthy) was selected as the most statistically significant covariate during the forward covariate selection, after which age became no longer significant.

Age and health status are strongly correlated. Healthy subjects age ranges from 18 to 55 years with median of 39 years, whereas patients ranged from 57 to 89 years old with a median of 77 years. Therefore, confounding of health status with age cannot be ruled out.

Model diagnostics indicated that the final model characterised the observed acoramidis concentration data and the inter-individual variability across all included studies reasonably well. Model parameters were precisely estimated, with relative standard error <31% for the key PK parameters except the food effect on D1, which had a relative standard error of about 50%.

Exposure-Response Analyses

E-R relationships for acoramidis were identified for endpoints including %CfB TTR at month 30, frequency/rate of CV hospitalisations, and %CfB NT-proBNP at month 30. %CfB TTR at month 30 was associated linearly with increasing acoramidis exposure (AUCss). This measure of efficacy reflects the intended pharmacodynamic action of acoramidis to stabilise and increase circulating serum TTR, the physiological protein that therapeutically mitigates the progression of ATTR-CM. This PD endpoint served as a substitute predictor variable in E-R modelling and analysis for other endpoints such as probability of ACM, CfB 6MWT at month 30, and time-to-event survival modelling for ACM where no direct E-R relationship could be shown to be statistically significant. The failure of these endpoints to achieve statistically significant model regressions against acoramidis exposure may have been due to survival bias: a small subset of ATTR-CM patients contributed to the analysis dataset at month 30 compared to day 28. This limited the number of patients with measured acoramidis concentrations and the exposure ranges in datasets for which response endpoints were measured. For instance, in Study

AG10-301 only 136 of 421 acoramidis-treatment patients had at least one acoramidis concentration measurement. This limited the number of individualised, model-predicted exposure metrics that could be computed with the population PK model. Further, patients treated with acoramidis were exclusively treated with an 800 mg dose in studies AG10-202 and AG10-301, limiting the range of possible acoramidis exposures sampled in E-R modelling and analysis.

VPCs for the models generally showed they were adequately fitted, with model parameter uncertainty overlapping the confidence interval of observed means. The CV hospitalisation Poisson model had a less favourable VPC, with mutually exclusive simulated predictions from model parameter uncertainty and 95% CI for observed means over some exposure quartiles. This is likely due the to the non-uniform distribution of CV hospitalisations over the Cmaxss exposure metric, where a global trend is captured over all the data while locally sparse regions of the observed range of Cmaxss are poorly fitted by the model. After covariate analysis, the Cmaxss coefficient failed to achieve statistical significance by a small margin, likely due to the non-uniformity of the data while the identified covariates furosemide/torsemide, other diuretics, and age in combination significantly improved the model fit to the data.

Furosemide, torsemide, and other diuretics as concomitant medications were associated with increased CV hospitalisation events. This may be because patients prescribed diuretics have poorer cardiovascular function and are at increased risk of hospitalisation independent of acoramidis exposure.

Physiologically Based Pharmacokinetic Model

A PBPK model for Acoramidis, based on physicochemical, *in vitro*, and clinical data was developed for the purpose of assessing the DDI liability of Acoramidis on the exposure of the sensitive OAT3 substrates, pravastatin and methotrexate in healthy non-Japanese and Japanese subjects.

The PBPK model for Acoramidis was developed using the 800 mg Acoramidis-HCl single and multiple (BID) dose data from Clinical Study AG10-001. The final PBPK model recovered the plasma concentration-time profiles and exposure levels of Acoramidis at these doses to within 1.4-fold of observed data.

The PBPK model was then verified using 800 mg Acoramidis-HCl single dose data from Clinical Study AG10-004 in non-Japanese and Japanese subjects as well as sparse 800 mg Acoramidis-HCl BID data from Clinical Study AG10-201 in ATTR patients. The PBPK model was able to recover plasma concentration-time profiles and exposure levels of Acoramidis after single and multiple oral doses in these studies to within 1.3 – 1.5-fold of observed data (Clinical Studies AG10-004 and AG10-201).

For the PBPK modelling of Acoramidis, predictions were considered to be reasonably accurate, as exposures were within 1.5-fold of the observed data.

Nevertheless, it is considered that the PBPK model investigating OAT inhibition has low impact, as a dedicated *in vivo* DDI study with OAT1 and OAT3 substrate probes was performed, using acoramidis as perpetrator.

Pharmacodynamics

Acoramidis is an oral, potent, high-affinity TTR stabiliser that acts to inhibit the dissociation of tetrameric TTR. It was rationally designed, informed by human genetics and structural biology, to mimic the stabilizing effects of T119M, a disease-protective gene variant, through a unique mode of binding to TTR.

The *in vitro* and *in vivo* nonclinical studies in multiple species have described the targeted pharmacology of acoramidis. Biochemical studies have established interspecies sensitivity and

measured selectivity of acoramidis for TTR from various species. The results provide support for the acoramidis mechanism of binding to TTR, ability to stabilise the tetrameric form of both TTRwt and TTRv in serum and plasma and establishes appropriate target therapeutic exposures in human subjects.

In the studies provided, the clinical benefits of acoramidis, were accompanied by near-complete (≥ 90%) TTR stabilisation across the dosing interval, as measured by the two *ex vivo* assays (FPE and WB) performed in study AG10-301, a level of stabilisation that is higher than that achieved with tafamidis. In the third assay of TTR stabilisation, serum TTR level was found to be elevated at the first assessment post acoramidis treatment initiation (day 28), remained consistently elevated with acoramidis for the entire duration of the study, and was 42% higher than the level observed with tafamidis in participants who were allocated to blinded placebo but were also prescribed concomitant, open-label tafamidis during the study.

In both ATTRv-CM and ATTRwt-CM, a clinically meaningful treatment benefit in TTR level was observed in the acoramidis treatment group compared to placebo from the first measurement at day 28 through month 30.

The progressive rise in NT-proBNP observed over 30 months for placebo in study AG10-301 was nearly halved in the acoramidis treatment group. At month 30, a statistically significant treatment effect on NT-proBNP was observed favouring acoramidis, with the adjusted geometric mean fold -change from baseline reduced from 2.77 for placebo to 1.47 for acoramidis.

Studies AG10-001, AG10-005 and AG10-201 were multiple dose Phase 1 and Phase 2 studies in which the primary pharmacodynamics was evaluated and confirmed as well as the dose-effect relationship.

On study AG10-202, all subjects, regardless of genotype, showed increases in serum TTR observed values, change from baseline and percent change from baseline by day 14 and through subsequent time points (up to month 36). The majority of subjects with ATTRv-CM had serum TTR levels <20 mg/dL at baseline. These subjects showed larger absolute and percent increases over baseline and the majority reached normal levels of serum TTR by day 14, which were generally sustained through subsequent timepoints. The FPE assay results show near-complete (≥90%) *ex vivo* stabilisation of TTR in most subjects from day 14 through month 36.

The applicant stated that the therapeutic hypothesis that has driven the design and execution of the acoramidis development programme is that near-complete (≥ 90%) and sustained TTR stabilisation, above and beyond what is achievable with tafamidis (as demonstrated in three complementary stabilisation assays in both variant and wild-type ATTR-CM), will slow, or stop, ongoing amyloid formation, resulting in better clinical outcomes and further reduction in disease progression than tafamidis.

The applicant has provided sufficient data to support the primary pharmacodynamics of acoramidis, establishing a correlation between TTR levels, as a valid pharmacodynamic endpoint, and acoramidis dose and plasma concentration. Further analysis on the efficacy-related endpoints will be performed in section 3 of this assessment report.

Electrocardiogram measurements in healthy adult volunteers, who were orally dosed with single supratherapeutic doses of up to 1780 mg acoramidis (Study AG10-005), demonstrated a clearly negative relationship between plasma concentrations of acoramidis/acoramidis-AG and the placebo-corrected change-from-baseline in QT interval corrected for heart rate (HR).

In the PK/PD sub-study of AG10-301, 99.2% (118/119) participant had acoramidis exposure values on day 28, 1 hour postdose < 27,500 ng/mL, the concentration up to which a QTc effect can be excluded based on the concentration-QTC analysis, while 1 participant had a value of 38,600 ng/mL. However,

there was no effect of acoramidis on the QTc interval in this participant. The participant's QTcF was 463 msec at baseline (D1). On day 28, participant had QTcF values of 441 msec (predose) and 461 msec (1 hour postdose). Centrally read ECGs in AG10-301 did not identify evidence of any clinically relevant drug-induced QT prolongation in the context of the trial.

The totality of data from *in vitro, in vivo,* and clinical studies excludes any clinically relevant effect on cardiac repolarisation.

Off-target activity was not detected when acoramidis at a concentration of 100 μM was tested in the Panlabs/Eurofin panel of receptors, enzymes and ion channels. Acoramidis did not inhibit COX enzymes or bind to thyroid hormone nuclear receptor at the tested concentration. No effect on vitamin A levels of related functions, as well as clinically manifestations of effects on thyroid function.

No pharmacodynamic interactions were studied and no information regarding PD-dependent DDI was provided by the applicant. Given the mechanism of action of acoramidis, some potential effect on thyroxine binding ability of TTR, alteration in TSH levels or any interference with hypo- or hyperthyroidism patients could be plausible, however the applicant has presented data that does not support any of these effects. Therefore, interaction with thyroid modulating medicines is not foreseen.

The AG10-301 allowed for the ex vivo evaluation of participant samples with different genotypes, confirming TTR stabilisation effects. On this study, the V30M mutation was not represented, which is the most common variant in Europe. Although the stabilisation effect on V30M was evaluated in the non-clinical setting, the applicant was asked to discuss the limited data on the most common European variant. The applicant states that, although the V30M mutation is the most common in the general ATTR population, that is not the case in the ATTR-CM phenotype. Acoramidis has been tested in two V30M variant patients. Evidence of TTR stabilisation by acoramidis was demonstrated in one participant with V30M in study AG10-201 who received acoramidis and in screening samples from one participant with V30M in study AG10-301 who was randomised to the acoramidis treatment group. In study AG10-201, the participant was treated with 800 mg BID dose of acoramidis. All three measurements of TTR stabilisation (circulating prealbumin levels and ex-vivo stabilisation by FPE and WB) demonstrated target engagement and stabilisation. There was one V30M variant participant enrolled in the AG10-301 study, who was randomised to the acoramidis treatment group. Serum and plasma samples from this variant participant were collected at screening, and TTR stabilisation was tested following in vitro addition of acoramidis. Addition of 10 uM acoramidis achieved 81.7% stabilisation in the WB assay and 100.3% in the FPE assay. Near complete stabilisation of TTR (≥ 90%) was observed with acoramidis in in vitro experiments with blood samples collected from participants carrying pathogenic TTR variants. In Study AG10 301, the clinical benefits of acoramidis were accompanied by near-complete (≥ 90%) TTR stabilisation, which is the same magnitude in the several variants, evidenced by in vitro and ex vivo data, including the V30M variant. The applicant believes that, taken together, data supports a stabilizing effect of acoramidis on TTR variants, which in turn translate into clinical benefit in ATTR-CM patients. Taking into consideration the in vitro and ex vivo data from the clinical trial, the assumption of PD effect and efficacy in V30M mutation patients can be performed. As requested, the applicant has added to 5.1 section of the SmPC the specific variants of the patients included in the clinical study (AG10-301 study).

The applicant has supported the PK/PD rationale and correlation to efficacy with the results from studies AG10-001, AG10-005, AG10-201 and AG10-301.

In the PK-PD Correlation Report for Study AG10-001, PD measurements of FPE and Western Blots achieved essentially complete and sustained target engagement and stabilisation of TTR, respectively, as assessed ex vivo following repeat dosing of AG10 to all subjects administered the 800 mg q12h dose. As an in vivo reflection of TTR stabilisation, repeat administration of AG10 increased prealbumin levels following administration of multiple oral doses of 100 mg, 300 mg, or 800 mg AG10 q12h. In

measurements obtained 24 hours apart, a mean increase of 8% in circulating prealbumin concentration was observed. There was no consistent increase in prealbumin concentrations observed in subjects dosed with placebo. Since the circulating half-life of prealbumin is 2-3 days, measurements made 24 hours apart may not be predictive of clinically relevant steady state changes in prealbumin levels.

In study AG10-005, measurement of pharmacodynamic activity by the FPE assay confirmed target occupancy at all single doses tested in AG10-005. Complete target occupancy of TTR was observed at peak concentrations following each dose of AG10.

From study AG10-201, a PK-PD relationship analysis segregated by TTR mutation status showed that higher plasma concentrations of AG10 generally produced greater serum TTR changes in participants with ATTRm-CM than those with ATTRwt-CM, based on a limited number (n=11) of participants with ATTRm-CM. The larger increases in TTR observed in participants with ATTRm-CM may be partially due to lower baseline TTR levels in participants with ATTRm-CM compared to those with ATTRwt-CM.

Serum TTR level increases of ≥50% occurred twice as frequently in participants administered AG10 800 mg BID than for those administered AG10 400 mg BID, regardless of mutation status.

FPE and WB results confirmed the pharmacological mechanism of action and extent of TTR stabilisation resulting from treatment with AG10 at either the 400 mg BID or 800 mg BID dose. Both of these assays demonstrated near complete ex vivo stabilisation of the tetrameric form of TTR. The FPE assay results demonstrated lower intersubject variability in participants treated with AG10 800 mg BID than in participants treated with AG10 400 mg BID.

Participants treated with AG10 800 mg BID were more likely to show complete stabilisation of TTR (≥90%), associated with trough concentrations of AG 10 that remained above the desired target therapeutic concentration of 8 µM, than participants treated with AG10 400 mg BID.

On study the phase 3 ATTRibute-CM Trial (AG10-301), at the observed mean trough concentration of 2358.0 ng/mL (approximately 8 µM), near-complete (≥ 90%) stabilisation was achieved in the mITT population. This near-complete (≥90%) stabilisation was observed for both ATTRv-CM and ATTRwt-CM.

At the observed mean trough concentration of 2358.0 ng/mL (approximately 8 µM), near-complete (≥ 90%) stabilisation was achieved in the mITT population. This near-complete (≥90%) stabilisation was observed for both ATTRv-CM and ATTRwt-CM.

Regarding safety endpoints, single and multiple oral doses of AG10 up to 800 mg (study AG10-001) as well as supratherapeutic oral doses (study AG10-005) appeared to be safe and generally well-tolerated by the healthy adult subjects in the studies, without any safety signals of potential clinical concern. On study AG10-301, no PK correlation was performed to safety endpoints, with a median exposure to acoramidis was 35.42 months (mean 27.37 months) with a range of 1.1 to 36.8 months. The exposure-adjusted incidence rate for all TEAEs was 600.45 events per 100 subject-years. The highest exposure-adjusted incidence rates per 100 subject years were observed for the PTs of fall (25.46), acute kidney injury (11.82), cardiac failure congestive (10.31), fatigue (9.26), and dyspnoea (9.18). All subjects in the study had underlying cardiac dysfunction, most subjects with events of acute kidney injury had a history of chronic renal failure, and all but 2 subjects in the study were at or over the age of 65 years at baseline. The risk of fall increases with advancing age. Incidence of fall in the study is consistent with the background incidence of fall in elderly patients.

No specific correlation of plasma concentration and safety can be established with the data provided.

The recommended dosage is acoramidis 712 mg BID orally (equivalent to 800 mg acoramidis HCl BID). The dose administered in the Phase 3 studies was acoramidis HCl 800 mg BID, administered as two 400 mg tablets, each equivalent to 356 mg acoramidis (total dose of 712 mg acoramidis [active

moiety]). This dose was selected to represent the optimal combination of potential efficacy, safety, and tolerability based on nonclinical PK studies, data from the Phase 1, first-in-human, single ascending dose (SAD), and MAD study (Study AG10-001) conducted in healthy adult volunteers, and the Phase 2, repeat dose, dose ranging, safety, tolerability, PK, and PD study in ATTR-CM patients with NYHA Class II-III heart failure (Study AG10-201).

In Study AG10-201, dose-related increases from baseline in serum TTR and stabilisation of the tetrameric form of TTR were observed in participants administered 356 mg and 712 mg acoramidis (equivalent to 400 mg and 800 mg acoramidis HCl, respectively) BID.

Serum TTR level increases of ≥ 50% occurred twice as frequently in participants administered 800 mg acoramidis HCl BID than those administered 400 mg acoramidis HCl BID, regardless of mutation status. Participants treated with 800 mg acoramidis HCl BID were more likely to show near-complete stabilisation of TTR (≥ 90%) than participants treated with acoramidis HCl 400 mg BID.

At steady state, the 800 mg acoramidis HCl BID dose produced both mean and median trough acoramidis concentrations (2439.4 ng/mL and 2360.0 ng/mL) above the targeted acoramidis concentration of 8 µM (2340 ng/mL), as opposed to 400 mg acoramidis HCl BID (1841.3 ng/mL and 1955.0 ng/mL).

Oral administration of acoramidis for 28 days at both doses was generally well tolerated in the participants, and there were no acoramidis-related safety signals of potential clinical concern. There were no clinically important differences in the safety profile between the doses.

Based on these data, a dose of 800 mg acoramidis HCl BID was selected for Phase 3.

Among the TTR genotypes analysed, the most frequently observed variant was V122I (N = 24 in all studies). The frequency of the other variants included in phase 2 and 3 studies ranged from 1 to 5.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacokinetic section of this application is based on data from the Phase 1 and Phase 2/3 studies. Generally, the characterisation of the pharmacokinetics of acoramidis and its metabolite is appropriate. All outstanding issues were clarified, mainly regarding information in SmPC on the absence of data in renal impaired patients, clarification of the metabolic pathway of acoramidis, characterisation of acoramidis-AG PK in patients with renal impairment, further evidence of clinical irrelevance of the preclinical reported data on irreversible inhibition of CYP2C8 and CYP2C9 and therefore potential interaction with other molecules especially those with a narrow therapeutic index and the unknown effect of gastric acid reducing agents on the pharmacokinetics of acoramidis.

The clinical pharmacodynamics section was based on phase 2 and phase 3 studies and has adequately characterised the primary pharmacodynamic profile, including the PD correlation to the variants included in the studies. There are no outstanding issues raised regarding pharmacodynamics.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

The dose administered in the Phase 3 studies was acoramidis HCl 800 mg BID, administered as two 400 mg tablets, each equivalent to 356 mg acoramidis (total dose of 712 mg acoramidis [active

moiety]). The rationale to select a higher 800 mg BID over the 400 mg BID dose in the phase 3 study was mainly based on an expected higher efficacy.

In the Phase 2 study, AG10-201, acoramidis treatment increased serum TTR levels and brought these to within the reference range in all participants with available data, both wild-type and variant. Acoramidis also stabilised variant TTR-containing tetramers to a similar degree as wild-type. A PK/PD analysis by TTR mutation status showed that, in general, for participants treated with acoramidis, the percentage change from baseline in serum TTR levels was greater in participants with ATTRv CM (67 ± 42%; n = 11 with available data) than those with ATTRwt-CM (33 ± 20%; n = 21). This finding could be partly due to lower baseline serum TTR levels in participants with ATTRv-CM compared to those with ATTRwt-CM. Participants in the placebo arm had no change or decreased serum TTR levels from baseline.

In Study AG10-201, dose-related increases from baseline in serum TTR and stabilisation of the tetrameric form of TTR were observed in participants administered 356 mg and 712 mg acoramidis (equivalent to 400 mg and 800 mg acoramidis HCl, respectively) BID.

Serum TTR level increases of ≥ 50% occurred twice as frequently in participants administered 800 mg acoramidis HCl BID than those administered 400 mg acoramidis HCl BID, regardless of mutation status.

Participants treated with 800 mg acoramidis HCl BID were more likely to show near-complete stabilisation of TTR (≥ 90%) than participants treated with acoramidis HCl 400 mg BID.

At steady state, the 800 mg acoramidis HCl BID dose produced both mean and median trough acoramidis concentrations (2439.4 ng/mL and 2360.0 ng/mL) above the targeted acoramidis concentration of 8 µM (2340 ng/mL), as opposed to 400 mg acoramidis HCl BID (1841.3 ng/mL and 1955.0 ng/mL).

Dose response of efficacy was further analysed in the PopPK/PD analysis EIDO-PMX-AG10-2264 (based on data from Study AG10-201 final data set, interim data from Study AG10-202, and from Study AG10-301 final data sets). A total of 679 participants with ATTR-CM met the criteria for inclusion in the exposure-response analysis population for efficacy. The final exposure-response model for %CfB in TTR showed a positive correlation between acoramidis exposure (AUCss) and increased serum TTR relative to baseline at month 30. An increased exposure was associated with a decreased number of expected cardiovascular hospitalisations (with a small decrease in elderly patients and a positive correlation of an increased event rate with concomitant diuretics). The model indicated a small, positive relationship between increasing serum TTR by day 28 of treatment and increased CfB in 6MWT at month 30. In the final exposure-response model increased acoramidis concentrations were associated with decreases in %CfB NT-proBNP concentrations at month 30 of treatment. In the time to event models for all cause mortality the base model indicated decreasing hazard and thus increased survival probability with increasing serum TTR at day 28. Covariate analysis identified statistically significant effects of baseline.

These data reasonably indicate a dose response within the investigated dose range. Regarding efficacy the choice of the dose 800 mg over a 400 mg BID dose can be followed.

In the OLE study (AG10 202), as of 06 January 2023, the mean of percent change from baseline in serum TTR levels was 48% at month 45 compared with baseline in participants with available baseline and month 45 data. Results of the FPE and WB assays showed sustained, near-complete TTR stabilisation at trough concentrations of acoramidis in participants with ATTRwt-CM and ATTRv-CM through month 51 of treatment.

The applicant claims that there are no clinically important differences in the safety profile between the doses. This statement is difficult to prove as only limited information is available on the comparative

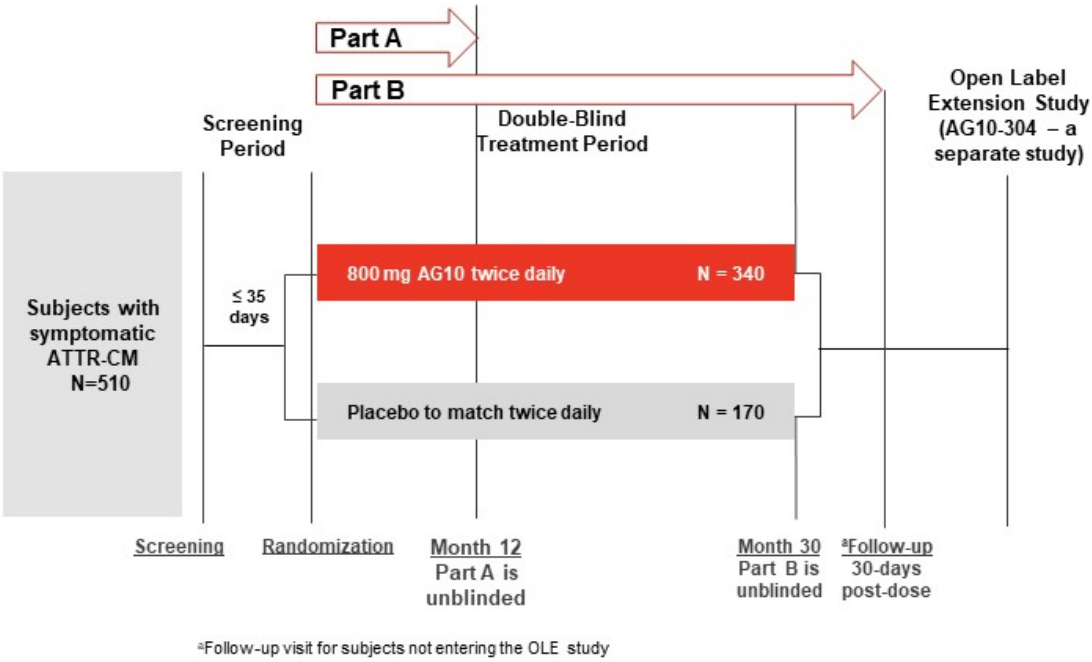
dose related safety profile in the target group of patients. In study 201 TEAEs and study treatment related TEAEs showed a dose response: Any TEAE 400 mg BID: patients: 10 (62.5%), number of events: 32; 800 mg BID: 11 (68.8), 36; placebo: 15 (88.2), 66. Study treatment-related TEAEs: 3 (18.8), 7; 6 (37.5), 10; 1 (5.9) 5 (Table in summary of clinical safety) with numbers of serious AEs reported too low to draw conclusions.

Similarly, the applicant has provided Exposure-Response Analyses of Acoramidis in Patients with Transthyretin Amyloid Cardiomyopathy (EIDO-PMX-AG10-2264, see above). In this analysis, the number of events was too low and therefore prohibitive to logistic modelling for the probability of a SAE and therefore was not pursued. At the end the issue of dose related safety is less relevant since a positive benefit risk balance has been demonstrated for the 800 mg BID dose in the pivotal phase 3 study.

2.6.5.2. Main study

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)

Figure 8: Study Schematic



Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; N = total number of participants in the study arm; OLE = open label extension
Note: To preserve blinding (to the treatment arm) throughout the study, the operating procedures were formalised for study conduct and the dissemination of results (AG10-301 CSR, Section 9.4.5). This Data Access Management Plan was finalised before Part A unblinding. The team conducting the analysis of Part B was not involved in the unblinded analysis of Part A.

Methods

- Study Participants

Patients were required to be ≥ 18 to ≤ 90 years of age at the time of randomisation. Patients had to have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype

(confirmed by genotyping), evidence of heart failure, with NYHA Class I-III symptoms due to ATTR-CM, able to walk ≥ 150 m on at least two 6MWT tests, and NT-proBNP level ≥ 300 pg/mL and < 8500 pg/mL at Screening, and LV wall (interventricular septum or LV posterior wall) thickness ≥ 12 mm. Participants were not eligible to participate in the study for reasons including, but not limited to: a confirmed diagnosis of light-chain (AL) amyloidosis; acute myocardial infarction, acute coronary syndrome, coronary revascularisation, stroke or transient ischemic attack within 90 days prior to Screening; or eGFR < 15 mL/min/1.73 m2 at Screening.

The eligibility criteria are largely acceptable and using positive technetium-99m-pyrophosphate or -bisphosphonate scan to replace biopsies is in line with current state of the art diagnostic workup (e.g. ESC position statement: European Heart Journal (2021) 42, 1554–1568), in addition to Echocardiographic/CMR criteria that were also a requirement of the inclusion criteria. The criterion of "NYHA Class I-III symptoms due to ATTR-CM" required further explanation since patients at NYHA I are usually considered asymptomatic at rest or at exercise. The applicant was asked to comment on which symptoms were expected and documented in patients with NYHA I. The rate of patients with hereditary forms of ATTR was low and similar in NYHA I and at a more advanced stage of the disease. Polyneuropathy did not appear to have been a reason to consider patients at NYHA stage I as symptomatic as o participants in NYHA Class I had amyloid polyneuropathy. The applicant clarified that the term „symptomatic" in these patients was related to history of symptomatic disease rather than symptoms at the time of randomisation. History of cardiovascular involvement included but was not restricted to atrial fibrillation, heart failure events, conduction disorders, but also coronary artery disease events are mentioned and history of stroke. It is not clearly stated that all of these patients had symptomatic disease at the time of randomisation as suggested by the inclusion criterion „NYHA Class I-III symptoms due to ATTR-CM". Upon request the applicant has made clear in section 5.1 of the SmPC whether patients at randomisation belonged to NYHA stage I-III and were symptomatic or had a history of symptomatic disease. Furthermore, the applicant also included the information on whether patients held mutated or wild-type TTR. In addition, it was also highlighted in section 5.1 of the SmPC that a lower response of NYHA Class III patients is observed as compared to the other classes.

Subgroup analyses indicated consistent numerical trends favouring NYHA I and NAC Stage I patients over a broad range of primary and secondary endpoints indicating that whether patient had currently symptomatic disease or were included based on a history of signs or symptoms of disease had no impact on the result.

No upper limit was predefined for the 6-MWT which might lead to ceiling effects in good performers at baseline. Evaluations for the results on the 6-MWT by baseline performance are expected. NT-proBNP levels ≥ 300 pg/mL at screening did not differentiate between whether patients had atrial fibrillation (57.8%) or not. It is not an issue of concern since other criteria (e.g. inclusion criterion 4) sufficiently ensured that heart failure associated with amyloidosis was an issue in the patient´s history. However, it may be relevant for the analyses of NT-proBNP as an efficacy parameter. The applicant provided efficacy results for NT-proBNP in the pivotal study, differentiating between patients with/without atrial fibrillation at baseline and further providing analyses of the impact of persistent vs. paroxysmal atrial fibrillation and for those patients that developed atrial fibrillation de novo during the study. As expected, atrial fibrillation appeared to have an impact on the results for NT-proBNP. For example, in patients with no atrial fibrillation at baseline an no atrial fibrillation as a TEAE during the study, only a small/no increase in NT proBNP from baseline to month 30 was observed in patients receiving acoramidis (mean/median). Patients who newly developed atrial fibrillation TEAE during the study had a more pronounced increase. As outlined by the applicant, the somehow lower rate of atrial fibrillation TEAEs as observed in the Acoramidis group may have contributed to the difference for the secondary endpoint NT-proBNP between the treatment arms. However, most of the effect on NT-prBNP was not

attributable to such indirect pathways. Irrespectively of the analysis sets (patients with/without atrial fibrillation at baseline, separation by type of atrial fibrillation, with/without TEAEs of atrial fibrillation), there was a consistent increase in NT proBNP over time in the placebo group over 30 months that was not or to a much lesser degree observed in the acoramidis arm suggesting (among others) functional cardiac improvements on myocardial wall stress among other possible factors that might contribute.

Tafamidis was not allowed during the first year of treatment over the first year, patisiran (within 90 days) and inotersen (within 180 days) were also not allowed. Albeit understandable for the demonstration of efficacy, treatments not allowed during the study are reflected in the SmPC.

- Treatments

Patients were allocated in a 2:1 ratio to either acoramidis 800 mg BID or matching placebo BID for a 30-month treatment duration.

After the first 12 months of study duration patients were able to add tafamidis if available at the study local site as per SmPC.

- Objectives

To determine the efficacy of acoramidis in the treatment of patients with symptomatic ATTR CM by evaluating the difference between the acoramidis and placebo groups in the combined endpoint of all cause mortality, the cumulative frequency of CV-related hospitalisation, change from baseline in NT proBNP, and change from baseline in 6MWD.

- Outcomes/endpoints

Primary endpoint: The primary endpoint was the hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalisation, as adjudicated by the CEC, difference in change from baseline in NT-proBNP (≥ 500 pg/mL), and difference in change from baseline in 6MWD over a 30-month fixed treatment duration.

Key secondary endpoints: The key secondary endpoints were:

- Change from baseline to month 30 of treatment in 6MWD.
- Change from baseline to month 30 of treatment in KCCQ-OS.
- Change from baseline to month 30 in serum TTR level (an in vivo measure of TTR stabilisation).
- All-cause mortality by month 30, including death due to any cause, heart transplant, or CMAD.

Several amendments were made on the definition of the primary and secondary endpoints while the study was ongoing:

Both key changes to the primary endpoint (inclusion of 6-MWD and of change in NT-proBNP, amendment 5 and 6) were clearly discouraged during the scientific advice for several reasons. A hierarchical endpoint with all-cause mortality and cumulative frequency of CV-related hospitalisation is considered not optimal but acceptable in this therapeutic area. Additional analyses based on first events are important to further analyse and understand the data. Change in NT-proBNP has not been accepted by the CHMP at the time of the scientific advice. Among others the predictive value in the context of acoramidis has not been demonstrated. Furthermore, inclusion of 6-MWD as a component was discouraged even if it may be a relevant secondary endpoint to assess functional capacity. Little additional information was expected since 6-MWD was already to be assessed by the part A analysis. Even if amendment 5 was implemented prior to unblinding of the study for analysis of Part A data (including analyses for 6-MWD), blinded results on variability for 6 MWD were available and it cannot

be excluded that informed guesses were possible based on unblinded data, e.g., by analysing correlations between PD endpoints and 6-MWD. Protocol amendment 6 was introduced after unblinding of part A when the results on Part A 6-MWD were available, allowing a guess on the final result for this component.

In conclusion, it was clear that the main assessment should be based on the primary endpoint as initially defined with all-cause mortality and CV-related hospitalisation as the sole components. Analyses based on endpoints as defined after amendment 5 and 6 were not accepted as key evidence for efficacy and this was raised in the first round of the assessment as a major objection. The applicant provided response was satisfactory:

- Overall, the analyses in the ITT were consistent with the predefined primary analyses in the mITT for the key efficacy endpoints: 2-step hierarchical analysis of ACM and CVH over a 30-month period, ACM or First CVH, ACM, Time to first CVH, and annualised frequency of CVH. Also, for the primary 4 component endpoint consistent results were reported. For all of these endpoints effect sizes and p values were reported that would have led to the same conclusion if ITT and not mITT had been predefined as the analysis set for the primary analysis.
- The issue that hierarchical dual combination of all-cause mortality and CV-related hospitalisation over a 30-month period (initially proposed primary endpoint) and Time to All-cause Mortality or First CV-related Hospitalisation were not included in the hierarchical testing strategy after amendment 5 and 6 is still formally an issue of concern. However, when taking the view that these endpoints were unambiguously considered the primary/key secondary endpoints relevant for the assessment by the CHMP, irrespectively of the applicant´s choice of a primary endpoint, the issue may become less relevant. In case these endpoints would not have shown nominal significant results, it would have raised major concerns. To the end the data on the dual endpoints, even if not included in the hierarchical testing procedures, can be accepted as confirmatory evidence.
- Exclusion of patients with eGFR < 30 but ≥ 15 mL/min/1.73 m^2 from the primary analysis had no relevant impact on the overall results. Reference is made to a Scientific Advice Procedure (Procedure No.: EMEA/H/SA/4038/1/2019/PA/III) where it was confirmed that enrolling a limited number of participants with severe renal impairment (eGFR < 30 but ≥ 15 mL/min/1.73 m^2), would be beneficial in providing preliminary information on the safety and tolerability of acoramidis and that this was an acceptable approach. This is acknowledged even if stratification for this subgroup would have been more consistent with conducting the primary analysis in a fully randomised population. The issue is not of high relevance considering the low number of patients included in this subgroup and the overall consistent results in the ITT and the mITT population.

Endpoint	mITT Population (N = 611)	ITT Population (N = 632)
2-step hierarchical analysis of ACM and CVH over a 30-month period	Win Ratio (95% CI): 1.464 (1.067, 2.009) p-value from F-S Method: 0.0182	Win Ratio (96% CI): 1.459 (1.055, 2.018) p-value from F-S Method: 0.0168
ACM or First CVH Hazard Ratio (95% CI)[a]	0.645 (0.500, 0.832) p-value: 0.0008	0.661 (0.516, 0.848) p-value: 0.0011

Endpoint	mITT Population (N = 611)	ITT Population (N = 632)
4-step hierarchical analysis of ACM, CVH, CFB in NT-proBNP and CFB in 6MWD over a 30-month period	Win Ratio (96% CI): 1.772 (1.402, 2.240) p-value from F-S Method: < 0.0001	Win Ratio (96% CI): 1.763 (1.399, 2.220) p-value from F-S Method: < 0.0001
ACM Hazard Ratio (96% CI)[a]	0.772 (0.532, 1.121) p-value: 0.1543	0.762 (0.533, 1.089) p-value: 0.1184
Time to first CVH Hazard Ratio (95% CI)[a]	0.601 (0.451, 0.800) p-value: 0.0005	0.611 (0.461, 0.809) p-value: 0.0006
Annualised frequency of CVH Relative risk ratio (95% CI)[b]	0.496 (0.355, 0.695) p-value: < 0.0001	0.510 (0.368, 0.708) p-value: < 0.0001

It was also not entirely clear whether the definition of changes in diuretic therapy as proposed by the applicant at the time of the last scientific advice, where implemented. From the CSR it is understood that the following definition applied for primary endpoint events:

“The diagnosis and interventions at an EOCI visit were required to document that the purpose of the visit was for IV diuretic therapy for management of decompensated heart failure or for a primary diagnosis of heart failure, and the event did not otherwise meet the criteria for CV-related hospitalization.” It is understood that only new administration of i.v. diuretics were accepted to qualify for an endpoint event but no other changes in diuretic therapy (oral or i.v.). The applicant confirmed the definition of the EOCI visit as applied in the study, which is acceptable.

- Sample size

The primary analysis population included subjects with baseline eGFR ≥ 30 mL/min/1.73 m2 (i.e., subjects with baseline eGFR < 30 mL/min/1.73 m2 will be excluded from the primary analysis population). It is estimated that approximately 10% of subjects will have baseline eGFR < 30 mL/min/1.73 m2. Sample size calculations are based on two-sided alphas = 0.01 for Part A and 0.04 for Part B.

Part A: The sample size calculation for the primary endpoint in Part A is based on the following assumptions: two-sided alpha = 0.01, power = 0.9, normally distributed data per group, equal within group standard deviations.

Part B: The power for Part B was originally estimated based on the primary endpoint of a hierarchical combination of All-cause mortality and CV-related hospitalisations over a 30-month treatment period. The test statistic for the combined endpoint is Finkelstein and Schoenfeld’s (Finkelstein 1999) adaptation of the generalised Gehan Wilcoxon test (and will be referred to as the Finkelstein-Schoenfeld test). Simulations based on estimates of mortality and CV-related hospitalisations from ATTR-ACT result in greater than 90% power with two-sided alpha = 0.04 with total N = 460 (= 0.9*510, i.e., after excluding 10% of subjects with baseline eGFR < 30 mL/min/1.73 m2) for the Finkelstein-Schoenfeld test to reject the null hypothesis that neither All-cause mortality nor CV-related hospitalisations is different between acoramidis and placebo. Simulations assumed an All-cause mortality rate of 40% for placebo with a hazard ratio of 0.7, mean number of CV-related hospitalisations by month 30 of 1.15 and 0.75 in the placebo and acoramidis groups, respectively.

Technically the sample size assessment is acceptable. Whether a 2:1 randomisation is an advantage (more patients on active treatment) or a disadvantage (e.g., comparative results in subgroups are less

robust), has not to be discussed in detail. It was planned to include approximately 510 participants which should provide a reasonable number for a clinical assessment.

- Randomisation and Blinding (masking)

Screening numbers were assigned consecutively through an IWRS portal after the participant signed the ICF. Participants who met eligibility criteria were randomised using permuted blocks and assigned a unique participant number through the IWRS. Participants were stratified at randomisation based on whether they had ATTRv-CM or ATTRwt-CM, with a targeted minimum of 20% of participants with ATTRv-CM. Participants were also stratified according to NT-proBNP level (≤ 3000 pg/mL versus > 3000 pg/mL) at Screening and by eGFR (≥ 45 mL/min/1.73 m^2 *versus* < 45 mL/min/1.73 m^2).

Blinding to individual participant treatment allocation was maintained for the participants, Investigators, CEC, DCC, Steering Committee, and Sponsor-designated site monitoring personnel throughout the study until the final participant had completed the expected month 30 or follow-up visit, the database was cleaned, and locked. The DMC was unblinded throughout and supplied periodic reports from the unblinded statistician at the data reporting centre. To preserve blinding (to treatment arm) throughout the study, the sponsor formalised operating procedures for study conduct and the dissemination of results, in collaboration with supporting organisations. This Data Access Management Plan was finalised before Part A unblinding and updated as appropriate throughout the study.

Of note, randomisation was not stratified by region or centre. The applicant has provided subgroup analyses for “US (~20%) vs Rest of the World (~80%)” but not for the EU separately. A subgroup analysis for the EU should be provided, since the subgroup “Rest of the World” is quite heterogeneous and includes centres across multiple continents. The applicant was asked to discuss this aspect and provided sensitivity analyses by Region EU in comparison to the entire study population. 355 out of 611 patients were recruited in the EU. Significance was not achieved for the 2-step hierarchical analysis of ACM and CVH in the EU sites but this is not unexpected. The results were overall consistent for the primary and key secondary analyses in the EU as compared to the overall population. The results on efficacy are relevant for the EU population as the table below shows.

Table 8: Clinical Outcome Measures for the EU Sites and Overrall Population, mITT Population

Endpoint	EU Sites (N = 355)	Overall (N = 611)
2-step hierarchical analysis of ACM and CVH over a 30-month period	Win Ratio (96% CI): 1.318 (0.851, 2.044) p-value from F-S Method: 0.1953	Win Ratio (95% CI): 1.464 (1.067, 2.009) p-value from F-S Method: 0.0182
ACM or First CVH Hazard Ratio (95% CI)[a]	0.644 (0.460, 0.903) p = 0.0107	0.645 (0.500, 0.832) p = 0.0008
ACM Hazard Ratio (95% CI)[a]	0.769 (0.486, 1.218) p = 0.2629	0.772 (0.542, 1.102) p = 0.1543
Annualized frequency of CVH Relative risk ratio (95% CI)[b]	0.507 (0.328, 0.783) p = 0.0022	0.496 (0.355, 0.695) p < 0.0001
Time to first CVH Hazard Ratio (95% CI)[a]	0.646 (0.443, 0.941) p = 0.0229	0.601 (0.451, 0.800) p = 0.0005

Abbreviations: 6MWT = 6-minute walk test; ACM = all-cause mortality; CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; CVH = cardiovascular-related hospitalization; eGFR = estimated glomerular filtration rate; EU = European Union; F-S = Finkelstein Schoenfeld; IXRS = Interactive Voice/Web Response System; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide

[a] Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWT as a covariate, and is stratified by randomization stratification factors of genotype, NT-proBNP level and eGFR level as recorded in IXRS.

[b] Negative binomial regression model with treatment group, randomization stratification factors of genotype, NT-proBNP level and eGFR level from IXRS, and the offset term is used to analyze the cumulative frequency of CEC adjudicated CV-related hospitalization.

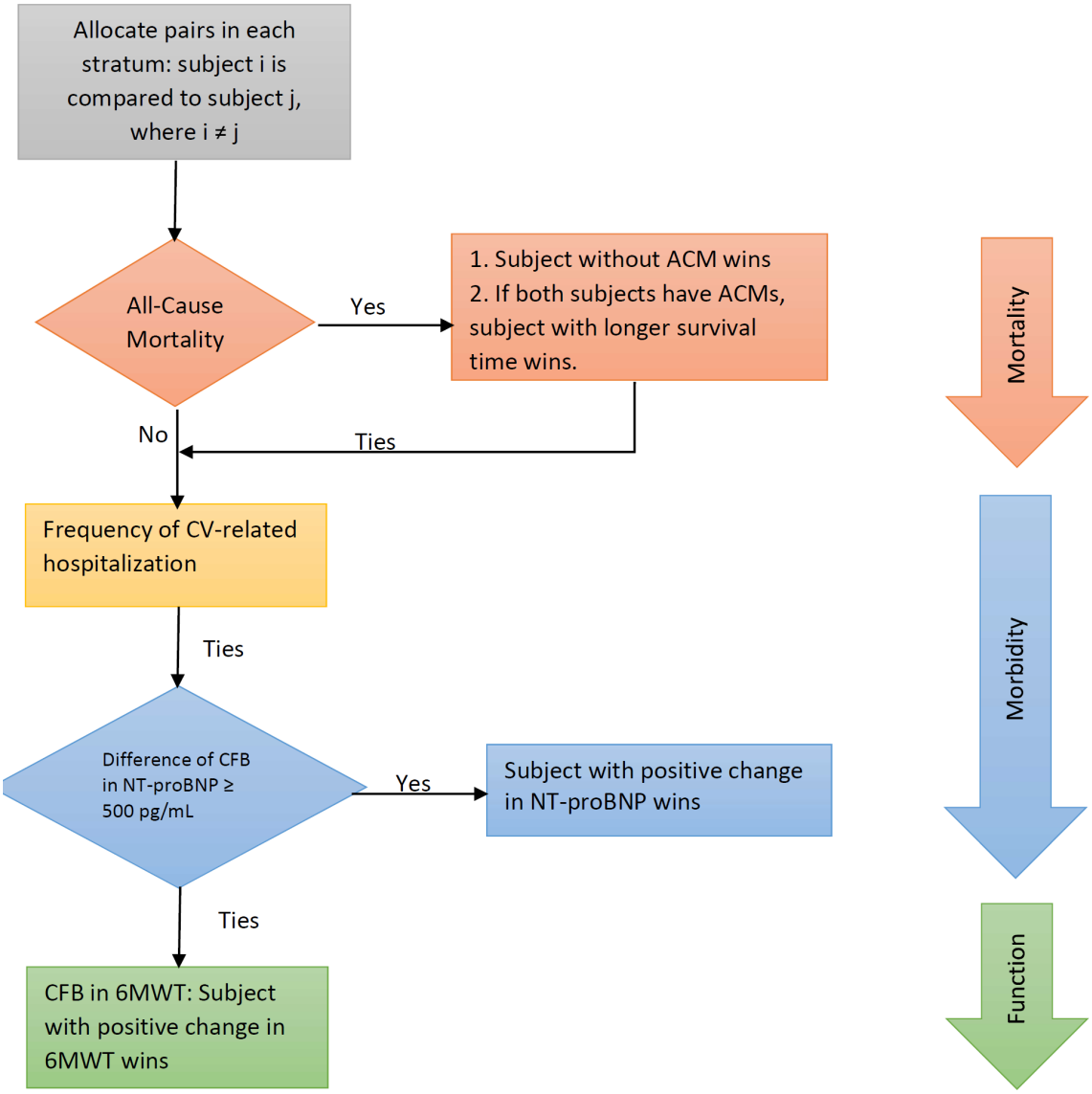
Source: Day 120 Response, Table 14.4.1.72, Table 14.4.1.73, Table 14.4.1.76, Table 14.4.1.78, Table 14.4.1.79, Table 14.4.1.80; AG10-301 CSR, Table 14.2.1.73; Table 14.2.1.88; Table 14.2.1.95; Table 14.2.1.138; Table 14.2.1.145

- Statistical methods

The primary endpoint for Part B is the hierarchical combination of All-Cause Mortality, cumulative frequency of CV-related hospitalisation as adjudicated by the clinical events committee (CEC), change from baseline (CFB) in NT-proBNP, and CFB in 6MWT over the 30-month duration.

Receiving a heart transplant or a cardiac mechanical assist device (CMAD) will be treated as death. For efficacy analyses, CV-related hospitalisations are those that were adjudicated as such by the CEC. A threshold of 500 pg/mL will be added in the comparison of CFB in NT-proBNP for each pair.

Figure 9: Finkelstein-Schoenfeld Scoring Algorithm



1. Positive change in NT-proBNP can be a smaller increase or a larger decrease from baseline in paired comparison.
2. Positive change in 6MWT can be a smaller decrease or a larger increase from baseline in paired comparison.
3. The paired comparison for NT-proBNP and 6MWT will use last available non-missing pair for both subjects.
4. A score will be assigned to the subject i within each pair with the following rules: win (+1), tie (0), loss (-1).

The pairwise comparisons as identified in Figure 8 are done within each stratum prior resulting in a total of 8 strata (2X2X2) are identified below:

- ATTRm-CM or ATTRwt-CM (with a targeted minimum of 20% of subjects with ATTRm-CM),
- NT-proBNP level (>=3000 vs >3000 pg/mL),
- Renal function defined by eGFR (>=45 mL/min/1.73m2) at Screening

If there are 5 patients in any of the strata, the strata including ATTRm-CM will be combined and resulting in a total of 5 strata.

The p-value from F-S test will be presented. Win-Ratio (Pocock 2012) and its confidence intervals will be calculated to aid in interpretation of the results for primary efficacy analysis from the F-S scoring algorithm.

The stratified non-matched Win-Ratio method allocates all treated and placebo pairs within each stratum in the same hierarchical structure from F-S test. The win ratio (RW) will be calculated by adding all wins from treatment group and dividing it by all wins from placebo group. The standard error of log (RW) will be derived as: SE (log (RW)) = log (RW)/Z-score from F-S test. An approximate 95% CI of win ratio then can be estimated from confidence interval of log (RW).

Regarding the acceptance of the primary endpoint see above. The key endpoint for an assessment of efficacy does only contain all-cause mortality and CV hospitalisation, but not 6-MWD and change in NT-proBNP.

Regarding the proposed primary efficacy endpoint, the following comments are made:

The definition of the ITT/mITT population is principally not acceptable, as excluding patients without postbaseline efficacy evaluation may lead to bias. Nevertheless, as no randomised patients were actually excluded from the ITT/mITT population due to this reason, there are no further concerns.

The mITT population was the primary analysis population for efficacy endpoints and included participants who met the definition of ITT and had a baseline eGFR ≥ 30 mL/min/1.73 m^2. The rationale of excluding patients with eGFR < 30 mL/min/1.73 m^2 from the primary efficacy analyses was unclear and required explanation. For the ITT population, only analyses of all-cause mortality and CV mortality were included in the CSR. Analyses of other relevant primary and secondary endpoints in the ITT population and in the subgroup of patients with a baseline eGFR < 30 mL/min/1.73 m^2 were also provided. The results for the secondary endpoints in the ITT were consistent with the results in the mITT. This is expected given the low Number of patients with eGFR < 30 mL/min/1.73 m^2. Numerically, in patients with eGFR < 30 mL/min/1.73 m^2, most secondary endpoints were either similar in both groups or showed a numerical imbalance in favour of acoramidis with one exception: The frequency of CV-related hospitalisation per year (mean [SD]) was 0.75 (1.962) and 0.43 (0.667) in the acoramidis and placebo groups, respectively, numerically favouring placebo. The applicant´s interpretation that in participants with a baseline eGFR < 30 mL/min/1.73 m^2, acoramidis delayed the first occurrence of CV-related hospitalisation compared with placebo until month 17 was not in line with the results as presented in Fig 13 in Appendix to response to Question 104, suggesting the opposite. The applicant discussed the result in the context of a lower CV mortality as a confounding factor. While this is possible, the results in low numbers of patients should anyhow not be over interpreted. Overall, the data do not indicate a fundamentally different outcome in patients with eGFR < 30 mL/min/1.73 m^2.

For the primary analysis of the primary endpoint, it was described that a treatment policy strategy was applied and all available measurements of the components of the primary endpoint were used in the analysis regardless of whether or not participants discontinued study drug or initiated concomitant tafamidis. At the same time, it was described that the pairwise comparisons were performed at the last available visit where both participants had non-missing assessments. From the CSR it is understood that the vital status could be collected for all patients, so that all pairwise comparisons with regard to all-cause mortality were performed at month 30. Nevertheless, for the other components (CVH, NT-proBNP, 6MWD) measurements after premature study discontinuation prior to month 30 were missing and the missing values were not imputed in the primary analysis, leading to pairwise comparisons with regard to the non-fatal components at various different timepoints in the primary analysis. A summary of the last available visit at which the pairwise comparisons were performed in the primary analysis should be provided for each component separately. In this case, the primary analysis is considered a mixture of the treatment policy strategy (for patients with measurements after premature treatment discontinuation) and the while on treatment strategy (for patients without measurements after premature study discontinuation). The clinical plausibility and relevance of this analysis is questionable because comparisons were not conducted at a unified relevant timepoint; furthermore, the

measurements after premature study discontinuation (this also implies premature treatment discontinuation) may follow a different distribution as the measurements on treatment. Therefore, an analysis for the estimand truly using the treatment policy strategy for all intercurrent events with an appropriate imputation of missing data after premature study discontinuation had to be conducted. The applicant provided the distribution of timing at which a tie is broken for each pairwise comparison for each of the CV-related hospitalisation, NT-proBNP and 6MWD components in the hierarchical order of the primary endpoint in the F-S test and win ratio analysis. The majority of the comparisons determined by CV-related hospitalisation, NT-proBNP and 6MWD were based on late study phase data (i.e., CV-related hospitalisation data with follow-up ≥ 24 months and change from baseline values at month 30). Furthermore, the applicant provided additional sensitivity analyses for the F-S test and win ratio analysis of the primary endpoint with missing data in the components of CV-related hospitalisation, NT-proBNP and 6MWD imputed simultaneously. Overall, the results of the additional sensitivity analyses were consistent with those of the primary analysis.

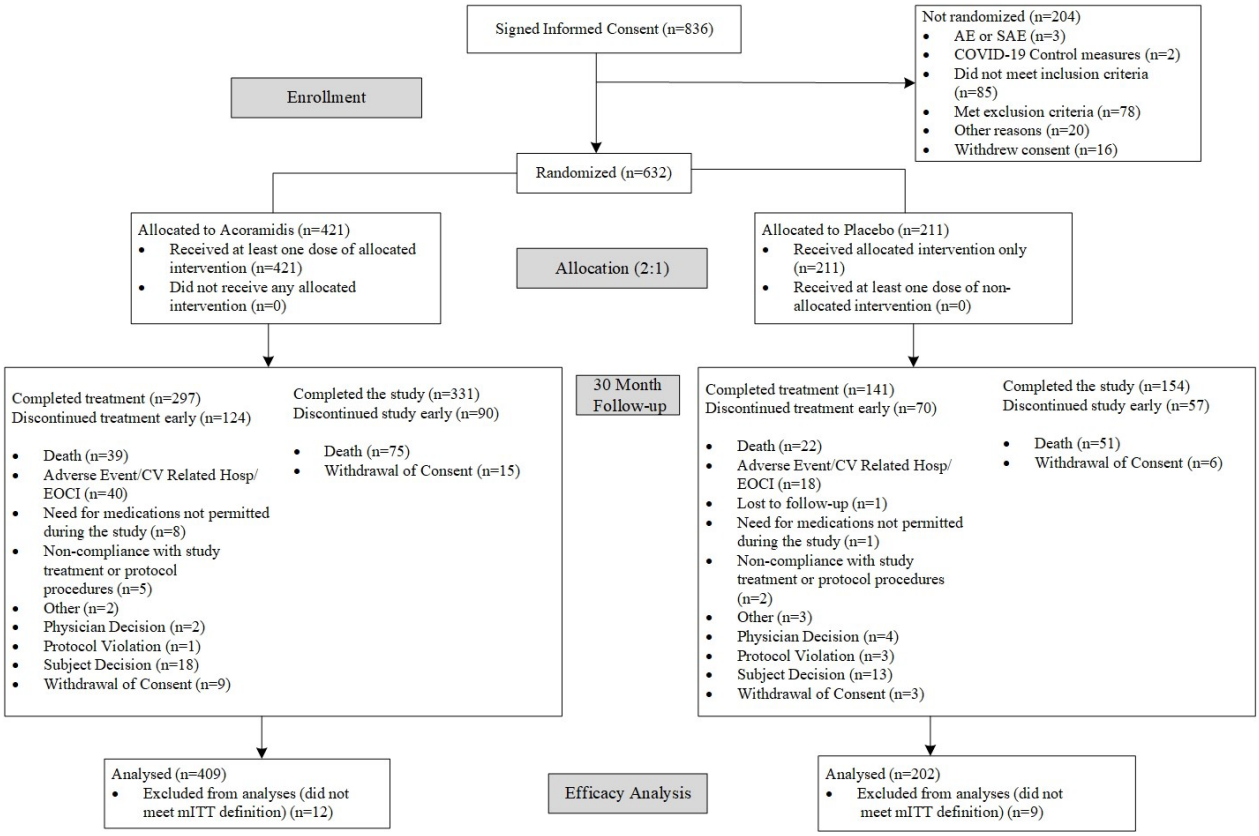
The applicant has conducted several sensitivity analyses of the primary endpoint to examine the impact of missing data on the interpretation of results, including (1) for NT-proBNP and 6MWD: imputation of missing measurements due to CVH by resampling from the worst 25% in the same arm at a given visit, imputation of missing measurements due to early treatment discontinuation under MNAR using the J2R method, imputation of all other missing measurements due to protocol deviations or any other reasons under MAR and (2) for CVH: a two-stage multiple imputation process that follows the procedure for monotone missing data (Rubin 1987) for any missing CVH due to early study discontinuation. However, in each sensitivity analysis, only one component (CVH, NT-proBNP or 6MWD) was imputed according to the above rules.

The applicant provided the number and proportion of participants with mis-stratifications. Overall, the proportion of participants with mis-stratifications was small and the impact on the results should be negligible.

It was described that a supplementary analysis was conducted using the principal stratum strategy in which participants from the mITT population who initiated tafamidis were excluded (i.e., acoramidis only versus placebo only). However, simply excluding patients who initiated tafamidis during the study from the analysis does not comply with the principal stratum strategy. The principal stratification that targets the effect in the subpopulation that would not experience an intercurrent event (i.e., initiation of tafamidis) under either treatment arm (acoramidis or placebo) requires specific analysis approaches. Furthermore, as principal stratification targets a subpopulation that can generally not be identified upfront, it is generally of less regulatory relevance. Although the performed analysis does not target the principal stratum strategy, it may still provide supportive information.

Results

- Participant flow



- Recruitment

Recruitment period: 25 April 2019 (first participant enrolled) presumably until November 2020:

11 May 2023 (last participant last visit for safety follow-up)

- Conduct of the study

There were 6 global amendments. Major amendments have been made to the protocol, including change in primary endpoint and promotion of secondary endpoints regarding the hierarchical order of key secondary endpoints. Minor amendments included clarification in inclusion and exclusion criteria.

Regarding the acceptability of amendments 5 and 6 that changed the primary endpoint during the ongoing study, see above.

Overall, the protocol deviations were balanced but rather high with 46.0% of “Any Important Protocol Deviation”, 20.0% related to inclusion criteria and 17.7% to informed consent. An imbalance in the assessment of safety is noted with 4.9% in the Acoramidis group and 13.4% in the placebo group.

The applicant was asked to comment whether the high rate of informed consent related protocol deviations was equally distributed over all centres/areas or were attributable to single centres/areas and might indicate issues with the ethical principles of the conduct of the study. More details were provided on informed consent important protocol deviations by centres and countries. The number do not indicate clustering in single centres and the type of deviations does not indicate protocol deviations that might have had an impact on efficacy, safety or ethical conduct or the study.

- Baseline data

In the mITT population, the patient population was well representative for the target group of patients with 51% above 77 years of age, 91% being male and 90% with ATTRwt-CM. The majority of patients was in NYHA stage II (73 %) with only 11% in NYHA I. When applying the NAC ATTR staging system the majority (59%) was at stage I and only 9% in stage III indicating that preferably patients at earlier clinical stages were included. Accordingly, the mean duration of ATTR-CM was rather short (1.2 years (SD 1.205)).

Participants were stratified based on:

- whether they had ATTRwt-CM or ATTRv-CM (overall, wild type status was reported for 90.3% and variant status was reported for 9.7% of participants in IXRS);
- NT-proBNP level at Screening (overall, approximately two-thirds of participants had NT-proBNP ≤ 3000 pg/mL [65.6%] versus 34.4% of participants with NT-proBNP > 3000 pg/mL) and
- eGFR at Screening (overall, most participants [84.6%] had screening eGFR ≥ 45 mL/min/1.73 m^2 versus 15.4% of participants with eGFR < 45 mL/min/1.73 m^2).

No notable imbalances were observed between the treatment groups by stratification factors and the study population was representative of the overall population with ATTR-CM at the time of study conduct.

In the mITT population, participant ATTR-CM diagnosis and history were generally well balanced between the treatment groups. Overall, 56 participants (9.2% of mITT population) had ATTRv-CM, and 62.5% of these 56 participants were V122I. Overall, four participants were homozygotes for the TTR mutation (all V122I). Most participants, 464 (75.9%) were diagnosed non-invasively without endomyocardial biopsy. Overall, 57.8% of participants had a medical history of atrial fibrillation, 18.8% of participants had a permanent pacemaker placed, and 43.4% of participants had prior carpal tunnel release surgery.

Genetic status was based on the eCRF and may differ from gene status from IXRS stratification factor, which was entered at the time of randomisation based on the information available to the Investigator at that time. This difference seems to be unavoidable.

Patients had typical disease characteristics with 57.8% with atrial fibrillation,18.8% and 6.7% with a permanent cardiac pacemaker/ICD. Renal disease was diagnosed in 28.8%, Amyloid Polyneuropathy in only 2.8% of patients. Almost all patients received diuretics (94.8%).

The mean proportion of tablets taken of the expected number was high (0.97 overall and in each treatment group). The median duration of treatment was similar in the acoramidis and placebo treatment groups (29.47 versus 29.44 months, respectively). A total of 107 participants (17.5% of mITT population) received tafamidis (tafamidis drop-ins) at any point during the study (i.e., before or after the month 12 visit). In the Safety Population, nine participants (acoramidis: seven; placebo: two) initiated tafamidis prior to the month 12 visit and were discontinued from study drug, per protocol. Ninety-eight participants (acoramidis: 54; placebo: 44 (note: 2:1 randomisation) initiated tafamidis on or after the month 12 visit. The number of participants who initiated tafamidis at any point during the study (i.e., before or after the month 12 visit) was greater in the placebo group compared to the acoramidis treatment group (22.8% versus 14.9%). Overall, the median time to initiation of tafamidis (relative to randomisation) and median duration of exposure to tafamidis during the study were 17.22 and 11.40 months, respectively.

The higher rate of patients receiving tafamidis on placebo than on acoramidis may reflect efficacy of acoramidis.

No information is available on patients with end stage cardiac disease at study entry. Some exploratory information might be collected from patients progressing to end stage disease (NYHA IV) during the course of the study. The applicant was asked to comment on the tolerability of acoramidis in such patients after deterioration. A brief summary on the numbers of patients that happened to deteriorate to NYHA class IV during the study was provided. The number of deteriorations was numerically slightly lower in the Acoramidis as compared to the placebo group (3.3 vs. 4.3%). For those patients that experienced an endpoint event of CV-related hospitalisation, most commonly caused by worsening heart failure, survival rate at month 30 was numerically higher in patients receiving acoramidis ((62.4%) compared to placebo (57.4%).

The data do not raise concerns on maintaining treatment with acoramidis in patients with deterioration of heart failure.

The applicant proposes to include the following statement in the SmPC to section 4.2:

“There are limited clinical data in patients with NYHA Class IV.”

This is endorsed. The indication as currently proposed may not entirely reflect that no patients at NYHA stage IV were included in the study. It is currently not known, whether the conclusions on benefit risk can be extrapolated when initiating treatment in patients at end stage disease. Restricting the indication to patients at NYHA stage I – III could be understood in a way that in patients deteriorating to stage IV during treatment continuation of acoramidis is not covered by the indication. However, the sparse data available do not indicate that discontinuation of acoramidis in these patients is warranted. The statement as proposed is therefore sufficient in the context of a non-restricted indication.

- Numbers analysed

Table 9: Baseline Assessments of Selected Key Secondary and Other Secondary Endpoints, mITT Population

	Acoramidis N = 409	Placebo N = 202	Overall N = 611
6MWD (meters)			
N	407	202	609
Mean (SD)	362.780 (103.5008)	351.510 (93.8277)	359.042 (100.4588)
KCCQ-OS			
N	408	202	610
Mean (SD)	71.73 (19.369)	70.48 (20.651)	71.32 (19.794)
Serum TTR (mg/dL)			
N	406	199	605
Mean (SD)	23.0 (5.58)	23.6 (6.08)	23.2 (5.75)
Western Blot TTR Percent Stabilisation			
N	118	48	166
Mean (SD)	25.85 (11.076)	22.88 (6.546)	24.99 (10.051)
NT-proBNP (pg/mL)			

	Acoramidis N = 409	Placebo N = 202	Overall N = 611
N	409	202	611
Mean (SD)	2865.3 (2149.64)	2650.1 (1899.48)	2794.2 (2071.20)

Abbreviations: 6MWD = 6-minute walk distance; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SD = standard deviation; TTR = transthyretin

- Outcomes and estimation

Primary Efficacy Endpoint

The applicant considers that primary endpoint was met and showed a statistically significant positive treatment effect of acoramidis relative to placebo ($p < 0.0001$).

Table 10: Finkelstein-Schoenfeld Analysis for Hierarchical Combination of All-Cause Mortality, CV-related Hospitalisation, Change from Baseline in NT-proBNP and Change from Baseline in 6MWD, mITT Population

	Acoramidis (N = 409)		Placebo (N = 202)
Participants with All-cause Mortality at month 30	79 (19.3%)		52 (25.7%)
Average CV-Related Hospitalisation Among Those Without All-cause Mortality at month 30 (per year)			
n	330		150
Mean (SD)	0.132 (0.3257)		0.293 (0.5751)
Median (Q1, Q3)	0.000 (0.000, 0.000)		0.000 (0.000, 0.404)
Min, Max	0.00, 2.03		0.00, 2.95
Details from F-S test			
Percent of Ties After All-cause Mortality		71.9%	
Percent of Ties After Cumulative Frequency of CV-Related Hospitalisation		44.9%	
Percent of Ties After Change from Baseline in NT-proBNP		14.7%	
Percent of Ties After Change from Baseline in 6MWD[a]		0.4%	
Test Statistic		5.015	
p value from F-S test		< 0.0001	

Abbreviations: 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; CV = cardiovascular; F-S = Finkelstein-Schoenfeld; max = maximum, min = minimum; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; Q = quartile; SD = standard deviation

There were ≤ five participants in certain strata within ATTRv-CM; thus, all strata within ATTRv-CM were combined resulting in a total of five strata.

[a] 6MWD is the distance achieved in a standardised 6MWT.

The win ratio for the pre-specified primary analysis was 1.772 (96% CI: 1.402, 2.240), indicating that an acoramidis-treated participant had a 77.2% higher chance of deriving a treatment benefit than a placebo-treated participant.

Table 11: Win Ratio Analysis for Hierarchical Combination of All-cause Mortality, CV-related Hospitalisation, Change from Baseline in NT-proBNP and Change from Baseline in 6MWD, mITT Population

	Acoramidis (N = 409)		Placebo (N = 202)
Details from Win Ratio			
Number of Pairs		28,794	
Pairs Won by All-Cause Mortality	4401		3880
Pairs Won by Cumulative Frequency of CV-Related Hospitalisation	5517		2894
Pairs Won by Change from Baseline in NT-proBNP	6723		2009
Pairs Won by Change from Baseline in 6MWD[a]	1705		1568
Total Wins	18,346		10,351
Total Ties		97	
Win ratio (Versus Placebo)		1.772	
96% CI of Win Ratio		(1.402-2.240)	

Abbreviations: 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide

[a] 6MWD is the distance achieved in a standardised 6MWT.

As discussed above, the primary endpoint is not accepted as key evidence to support efficacy. Neither NT-proBNP nor a win ratio for 6-MWD are accepted as components. The result is to a large degree driven by the cumulative frequency of CV-related hospitalisation and even more by the difference in NT-proBNP.

Table 12: Pockock Wins, Ties, and Losses at Each Level, mITT Population

	Total Participant Pairs			Win Ratio
	Wins	Ties	Losses	
All-cause Mortality	15.3%	71.2%	13.5%	
Frequency of CV-related Hospitalization	19.2%	42.0%	10.1%	
Change From Baseline in NT-proBNP	23.3%	11.7%	7.0%	
Change From Baseline in 6MWD[a]	5.9%	0.3%	5.4%	
Overall	63.7%		35.9%	1.8

Abbreviations: 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CV = cardiovascular; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
Note: Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis.
[a] 6MWD is the distance achieved in a standardized 6MWT.
Source: Table 14.2.1.142

The applicant states that the primary efficacy endpoint was primarily driven by the contribution of the clinical outcomes of all-cause mortality and frequency of CV-related hospitalisations as the majority of the ties (55% in the F-S test and 58% in the win ratio) were broken by the first two components in the primary analysis. This argumentation is not entirely followed, the major contributor to wins was NT-proBNP accounting for more than 1/3 of the wins counted.

The applicant provided several sensitivity analyses by using different thresholds for NT-proBNP, imputation of values and by excluding patients receiving Acoramidis. These sensitivity analyses had no relevant impact on the overall result but do not alter the general concerns associated with the endpoint as defined.

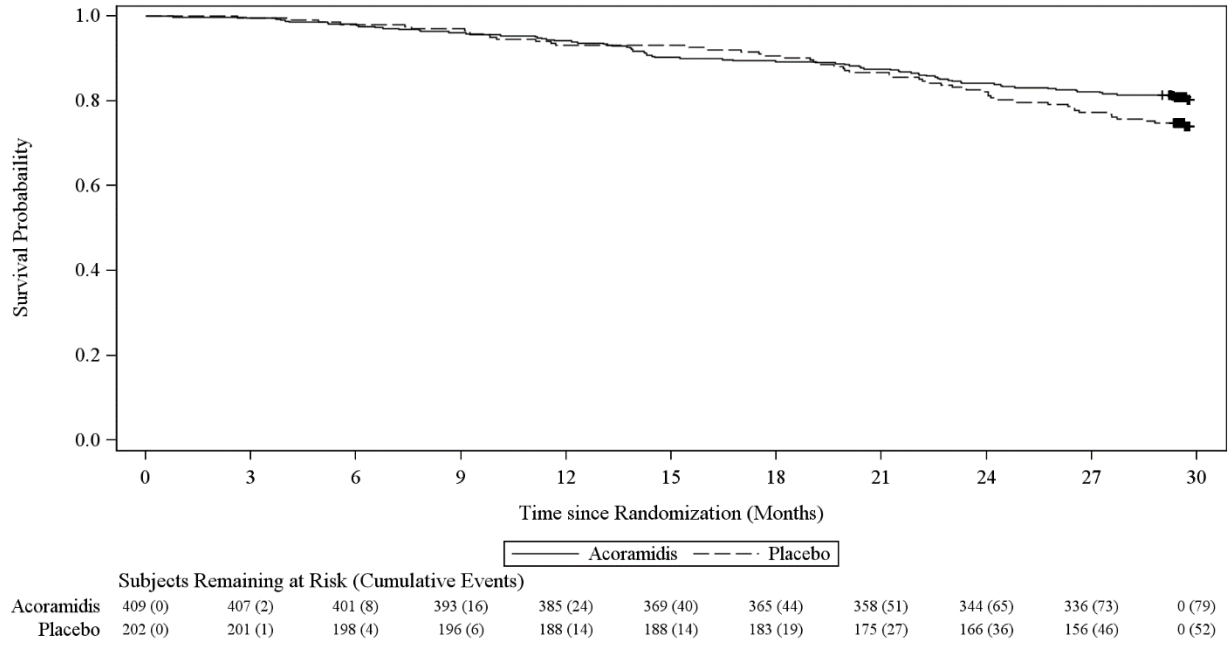
Summary: The primary endpoint was discouraged in two scientific advice procedures and the main assessment should be based on the primary endpoint as initially proposed, containing all-cause mortality and CV hospitalisation as components only.

Relevant secondary endpoints

All-cause Mortality

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

Figure 9: Kaplan-Meier Curve for Time to All-cause Mortality Over month 30, mITT Population



Numerically, mortality was lower in patients receiving acoramidis, but no significant improvement was observed for all-cause mortality. The pattern of the KM curves resembles in part to what has been observed with tafamidis (Maurer et al., N Engl J Med 2018;379:1007-1016) with no relevant difference over about 18 months and a spread in the curves thereafter. Crossing of the curves at earlier time points may not be overinterpreted but points to a cautious interpretation of the results at later time points.

The results were consistent for the ITT population. The analysis of CV mortality showed similar non-significant results. The Kaplan-Meier curves for time to CV-related mortality showed separation of the curves starting at month 18 and increasing in magnitude through month 30. The majority (104/131; 79%) of mortality events were CV-related. CV-related mortality was reported in 14.9% and 21.3% of participants in the acoramidis and placebo groups, respectively. The hazard ratio from the CV-related mortality Cox proportional hazards model for acoramidis versus placebo was 0.709 (95% CI: 0.476, 1.054; nominal p = 0.0889).

The analysis included mortality events and in addition heart transplant and CMAD (Cardiac mechanical assist device). While this is defendable, additional sensitivity analyses by excluding these two components were required. Two participants, both in the placebo group, had an event each of heart transplant and CMAD thereby meeting the endpoint of all-cause mortality without experiencing an actual death. Results of sensitivity analyses by excluding these events for the main pre-specified endpoints that included all-cause or CV mortality were consistent with the main analyses. In the Kaplan Meyer analyses separation of the curves for all-cause mortality was observed later after excluding these two events, starting at month 24, and increasing in magnitude through month 30 as compared to a separation starting at month 19 in the main analysis. This minor shift does not put the main analysis in question.

No results were presented for CV mortality in the ITT population. These data were requested to be provided during the procedure (see below).

Table 13: Summary of All-cause Mortality, mITT Population

	Acoramidis (N = 409)		Placebo (N = 202)
All-cause Mortality[a]	79 (19.3%)		52 (25.7%)
Total Deathb	79 (19.3%)		50 (24.8%)
CV-relatedc	61 (14.9%)		41 (20.3%)
Non-CV-related	18 (4.4%)		9 (4.5%)
Unknown	0		0
CMAD Implantation	0		1 (0.5%)
Heart Transplants	0		1 (0.5%)
Cox Proportional Hazard Model[d]			
Hazard Ratio (Versus Placebo)		0.772	
95% CI of Hazard Ratio		(0.542, 1.102)	
96% CI of Hazard Ratio		(0.532, 1.121)	
p value		0.1543	
Log-rank test[e]		0.0754	
Cochran-Mantel-Haenszel test		0.0569	
Time-Dependent Cox Model[f]			
Hazard Ratio (Versus Placebo)		0.774	

	Acoramidis (N = 409)		Placebo (N = 202)
95% CI of Hazard Ratio		(0.543, 1.104)	
96% CI of Hazard Ratio		(0.533, 1.123)	
p value		0.1577	

Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; CMAD = cardiac mechanical assist device; CV = cardiovascular; eGFR = estimated glomerular filtration rate; IXRS = Interactive Voice/Web Response System; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide

[a] All-cause mortality included all cause death, heart transplant, and CMAD implantation.

[b] Total death included CV-related and non-CV-related death.

[c] CV-related death included all adjudicated CV-related and undetermined cause death.

[d] Stratified Cox proportional hazards model included treatment as an explanatory factor and baseline 6MWD as a covariate, and was stratified by randomisation stratification factors of genotype, NT-proBNP level, and eGFR level as recorded in IXRS.

[e] Stratified log-rank test that was stratified by randomisation stratification factors of genotype, NT-proBNP level, and eGFR level as recorded in IXRS.

[f] Stratified Cox proportional model was performed with the addition of the time-dependent covariate for introduction of tafamidis.

The main outcome most relevant for the assessment are:

- The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period (primary endpoint as initially defined before amendments 5 and 6)) and
- Time to All-cause Mortality or First CV-related Hospitalisation.

It was not quite understood why these two endpoints were not included in a hierarchical testing strategy. For this very reason, formally, neither the initially proposed primary endpoint nor the first event analysis might be considered confirmatory to support the application.

In the ITT population, which included participants with eGFR< 30 mL/min/1.73 m^2, the risk of all-cause mortality was lower in the acoramidis treatment group compared to the placebo group (hazard ratio: 0.762, 96% CI: 0.533, 1.089; p = 0.1184, stratified Cox proportional hazard model). The all-cause mortality results in the ITT population were also examined using a stratified log-rank test (p = 0.0520) and a CMH test (p = 0.0390).

The 25% relative risk reduction in all-cause mortality observed in the mITT population was also observed in the 21 participants with eGFR< 30 mL/min/1.73 m^2 (acoramidis: 41.7%; placebo: 55.6%).

The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period

Numerically, statistical significance was achieved on the two-component (all-cause mortality and frequency of CV-related hospitalisations) F-S test, which demonstrated the superior treatment effect of acoramidis compared to placebo (nominal p = 0.0182; Table 14 and Figure 10).

Table 14: Finkelstein-Schoenfeld and Win Ration Analyses for Hierarchical Combination of All-cause Mortality and CV-related Hospitalisation, mITT Population

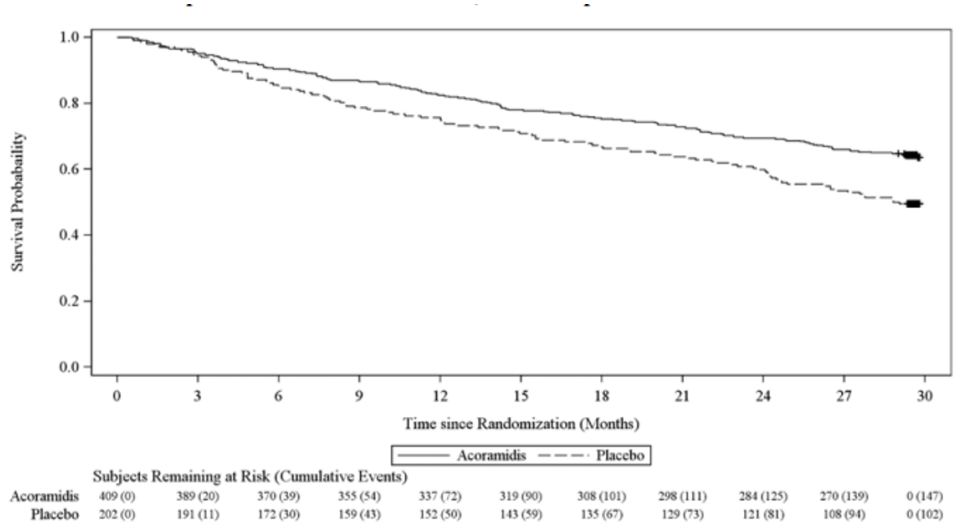
	Acoramidis (N = 409)		**Placebo (N = 202)**
Details From F-S Test			
Percent of Ties After All-cause Mortality		71.9%	
Percent of Ties After Cumulative Frequency of CV-related Hospitalization		44.9%	
Test Statistic		2.361	
p value From F-S Test		**0.0182**	
Details From Win Ratio			
Number of Pairs		28794	
Pairs Won by All-cause Mortality	4401		3880
Pairs Won by Cumulative Frequency of CV-related Hospitalization	5517		2894
Total Wins	9918		6774
Total Ties		12102	
Win Ratio (versus Placebo)		**1.464**	
95% CI of Win Ratio		**(1.067, 2.009)**	
Win Odds		1.245	
95% CI of Win Odds		(1.034, 1.499)	

Abbreviations: CI = confidence interval; CV = cardiovascular; F-S = Finkelstein-Schoenfeld; mITT = modified intent-to-treat
Source: Table 14.2.1.88

Time to all-cause mortality or first CV-related hospitalisation

The Kaplan-Meier curves for time to all-cause mortality or first CV-related hospitalisation started to separate at month 3 and this effect was sustained through to month 30 (Figure 10). The composite of time-to-first-event of all-cause mortality or CV-related hospitalisation was reported in 147 (35.9%) and 102 (50.5%) acoramidis and placebo-treated participants, respectively, corresponding to a 14.6% absolute risk reduction. A 35.5% hazard reduction in all-cause mortality or first CV-related hospitalisation at month 30 was observed in the acoramidis treatment group compared to placebo (hazard ratio: 0.645 [95% CI: 0.500, 0.832; nominal p = 0.0008].

Figure 10: Kaplan-Meier Curve for Time to All-cause Mortality or First CV-related Hospitalisation Over Month 30, mITT Population



Abbreviation: CV = cardiovascular; mITT = modified intent-to-treat
Source: Figure 14.2.1.56

The difference was mainly driven by first CV hospitalisations (see below):

The applicant provided the results for ITT endpoints:

- The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period

- Time to All-cause Mortality or First CV-related Hospitalisation

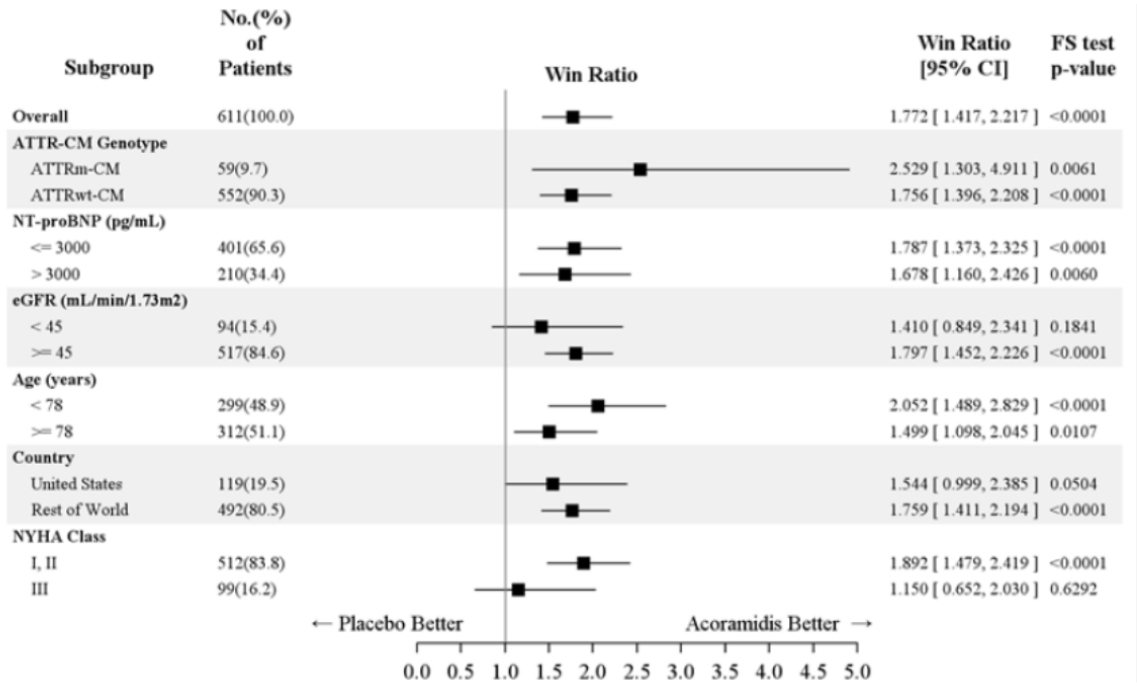
- CV related hospitalisation:

- On the 2-step hierarchical ACM and CVH over the 30-month period for ITT, the initial primary endpoint, both the mITT and the ITT results are statistically significant and considered relevant, favouring acoramidis.
- The supportive analysis of the individual ACM is less clear, and less clinically impressive, with only a 7% difference in mortality by the end of month 30 (20% acoramidis, 27% placebo). It apparently only detaches by the end of the second year of follow up and. The combination of ACM + First CVH is clearly driven by the First CV-Related Hospitalisation, where the two groups detach as early as 3 months, similar to the isolated First CV-Related Hospitalisation endpoint. Although it is not possible to confirm in this population (and the applicant does not discuss this either) it is possible that the fluctuations observed in the ACM along the first 21st months may be due to a lower mortality for all causes in the in-hospital patient. In fact, the hospitalised patient, independently from the cause of admission, may be studied for other conditions (that may even precipitate the worsening of the cardiac condition, such as a respiratory infection) and may be dealt with in a timely manner, preventing or delaying death. Both the number of events by month 30 and the time to event by the same timepoint favour acoramidis.

Subgroup analyses

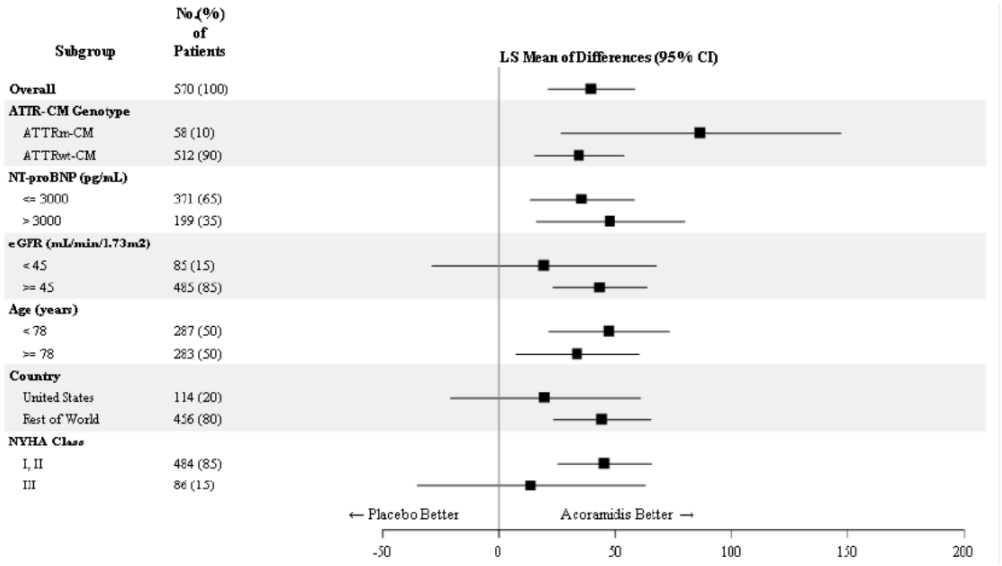
The applicant has provided subgroup analyses for the primary efficacy endpoint (Figure 11) and for secondary efficacy endpoints (presented here: 6 MWD: Figure 12, All-cause mortality, Figure 13, and cumulative rate of CV hospitalisations: Figure 14).

Figure 11: Finkenstein-Schoenfeld and Win Ratio Analyses for Primary Endpoint by Overall and Subgroup, mITT Population



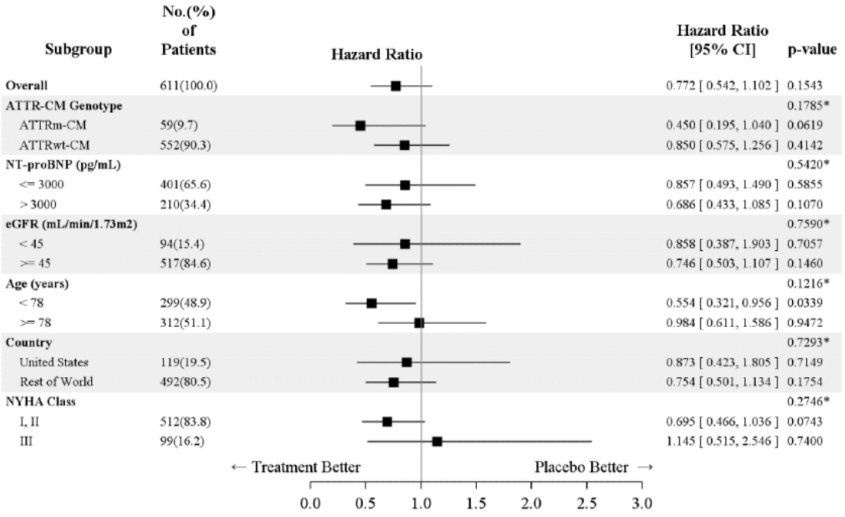
Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRwt-CM = wild-type ATTR-CM; CI = confidence interval; eGFR = estimated glomerular filtration rate; F-S = Finkelstein-Schoenfeld; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association
Source: Figure 14.2.1.1

Figure 12: Forest Plot for Change from Baseline in 6MWD (meters) to Month 30 by Overall and Subgroup, mITT Population



Abbreviations: 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRwt CM = wild-type ATTR-CM; CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least squares; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association
6MWD is the distance achieved in a standardized 6MWT.
Source: Figure 14.2.3.10

Figure 13: Forest Plot for Hazard Ration of All-cause Mortality by Overall and Subgroup Analysis, mITT Population

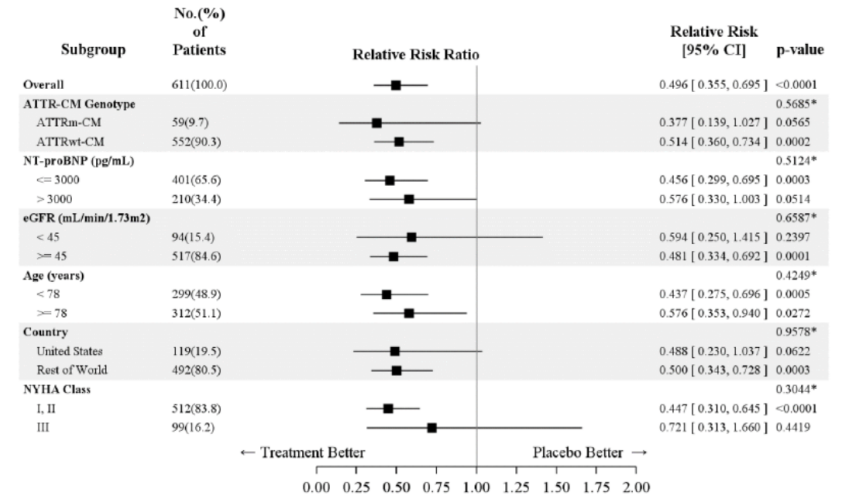


Abbreviations: 6MWD = 6-minute walk distance; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRwt CM = wild-type ATTR-CM; CI = confidence interval; CMAD = cardiac mechanical assist device; eGFR = estimated glomerular filtration rate; LS = least squares; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association

All-cause Mortality includes heart transplant, CMAD and all-cause death. * Hazard ratio and p value results are from stratified Cox proportional hazard model with model terms: treatment, baseline 6MWD, subgroup of interest, subgroup x treatment, subgroup x baseline 6MWD. If subgroup variable itself is stratification factor, then it will be removed from stratification variable list. ** P values with * are from testing the interaction of subgroup x treatment, and other p values are for testing the treatment difference at a given value of subgroup variable.

Source: Figure 14.2.1.53

Figure 14: Forest Plot for Relative Risk Ratio of Cumulative Frequency of Cardiovascular Related Hospitalization by Overall and Subgroup, mITT Population



Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRwt CM = wild-type ATTR-CM; CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association

* Negative binomial regression with treatment group, stratification factors, subgroup of interest, subgroup x treatment, and the offset term is used to analyze the cumulative frequency of CEC adjudicated CV-related hospitalization. ** P values with * are from testing the interaction of subgroup x treatment, and other p values are for testing the treatment difference at a given value of subgroup variable.

Source: Figure 14.2.1.57

Overall, the results were consistent for most subgroups with the exception of NYHA class III. For the primary 4-fold efficacy endpoint and for the 6-MWD, no efficacy was observed in patients with NYHA III, only little efficacy was observed for the cumulative frequency of CV hospitalisations.

For all-cause mortality, the point estimate was even in favour of placebo. The later finding is a bit puzzling since Table 14.2.1.81 of the study report provides a lower rate of deaths with acoramidis in patients with NYHA III:

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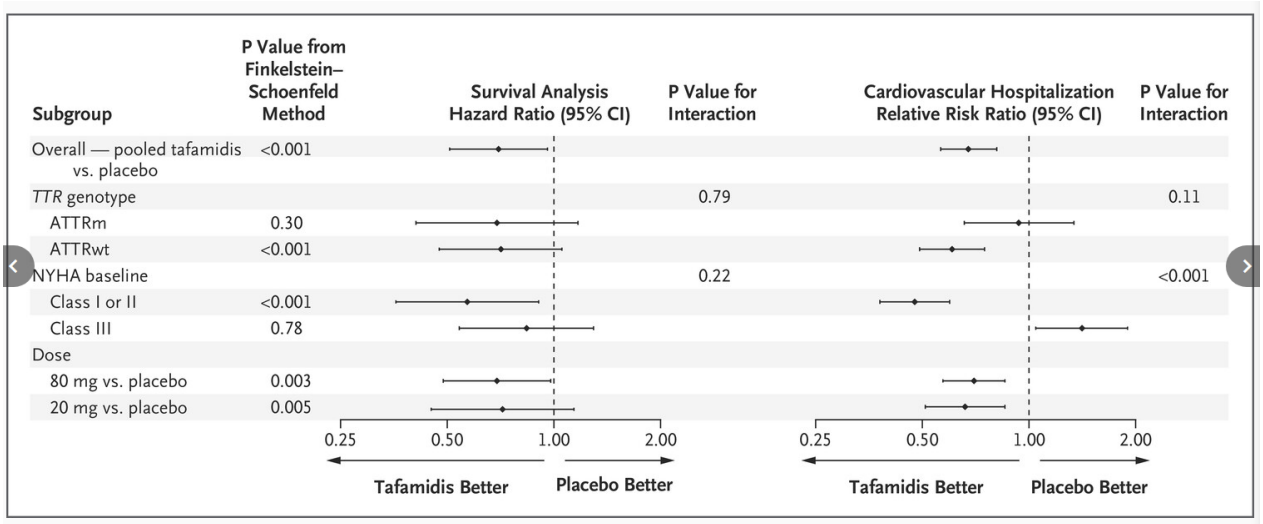
Table 14.2.1.81
Summary of All-Cause Mortality by Baseline NYHA Class
mITT Population

NYHA Class III	Acoramidis (N=70)		Placebo (N=29)
All-Cause Mortality [a]	20 (28.6%)		10 (34.5%)
Total Death [b]	20 (28.6%)		10 (34.5%)
CV-related [c]	16 (22.9%)		10 (34.5%)
Non-CV-related	4 (5.7%)		0
Unknown	0		0
Cardiac Mechanical Assist Device Implantation	0		0
Heart Transplants	0		0
Log-rank test [d]		0.6693	
Cochran-Mantel-Haenszel test		0.5926	

Further explained was required by the applicant and Kaplan Meier curves for mortality by NYHA category provided.

Results showing a lower/absent efficacy in patients with NYHA III for several endpoints are not entirely unexpected. A similar pattern has been observed with tafamidis (Figure 3, Maurer et al., 2018)

Figure 3 from Subgroup analyses for tafamidis for the dual primary endpoint and for cardiovascular Hospitalisation (Maurer et al., 2018)



For tafamidis it was concluded by the CHMP that a lower mortality in NYHA III patients might have contributed to a higher CV hospitalisation rate. The consistency of the result of a lower efficacy in patients with NYHA III for two medicinal products with the same mode of action appears to provide some robustness. Based on the data currently provided for Acoramidis this may not be a likely explanation. The consistent result of a lower/absent efficacy in patients at NYHA III need further discussion and analyses. Currently efficacy in these patients is not considered established.

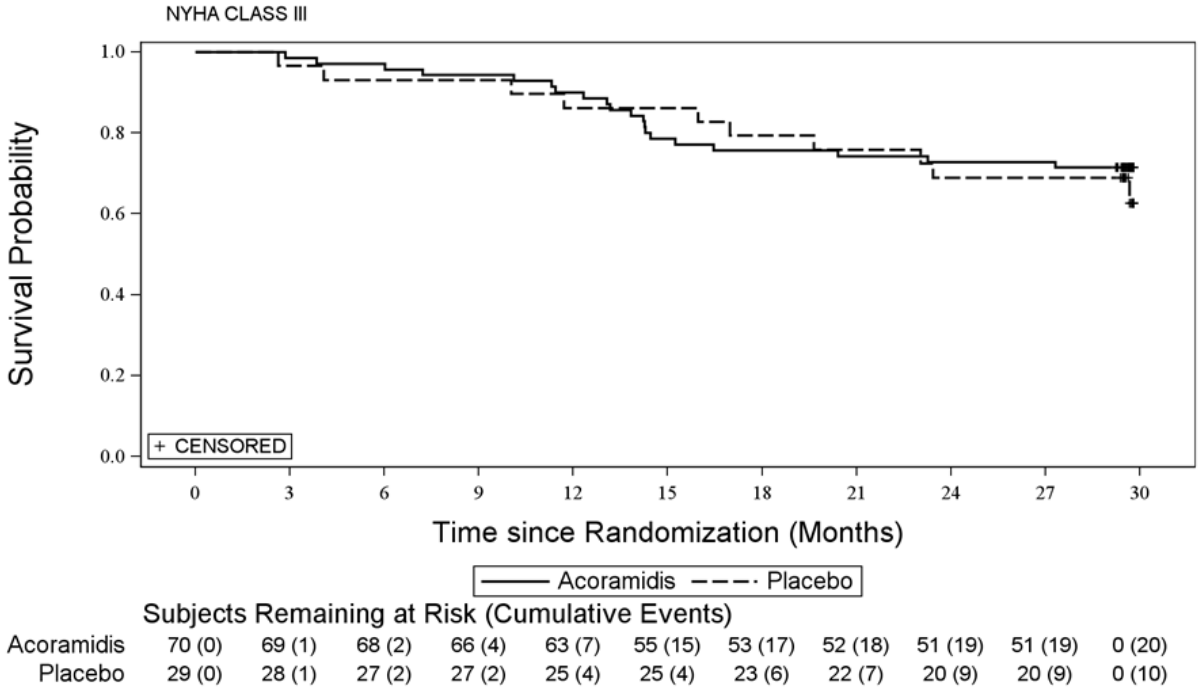
The applicant was asked to discuss efficacy in patients with NYHA III and provide the following additional data:

Analyses by subgroups NYHA III vs. NYHA II vs. NYHA I and by NAC ATTR Stage III vs. II vs. I for the following outcomes both for the ITT and the mITT population:

- The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period
- All-cause Mortality or First CV-related Hospitalisation.
- All-cause Mortality
- CV mortality
- First CV-related Hospitalisation.
- Cumulative Frequency of CV-related Hospitalisations (including recurrent events)
- 6-MWD

The applicant has provided the requested analyses by NYHA stage and NAC ATTR stage for key efficacy endpoints in the mITT and the ITT population. It is acknowledged that analyses should be interpreted with caution due to lower numbers of patients per subgroup and some numerical imbalances (e.g., sex and rate of patients with ATTRm-CM). However, the data consistently indicate lower efficacy in patients at NYHA stage III and NAC ATTR stage III as compared to patients at earlier stages or the disease. For example, there was no benefit for ACM or First CVH. A continuous trend to lower efficacy was consistent when comparing NYHA I over II to III. For NAC ATTR Stage, Stage I and II showed comparable results and only results in stage III indicated lower/absent efficacy. The numerically low /absent efficacy in morbidity/mortality related events, was accompanied by lower efficacy results both for 6-MWD and KCCQ-OS in NYHA III and NAC ATTR Stage III. Since patients were stratified according to NAC ATTR stage, this evaluation may possibly even provide more reliable data as compared to analyses by NYHA stage.

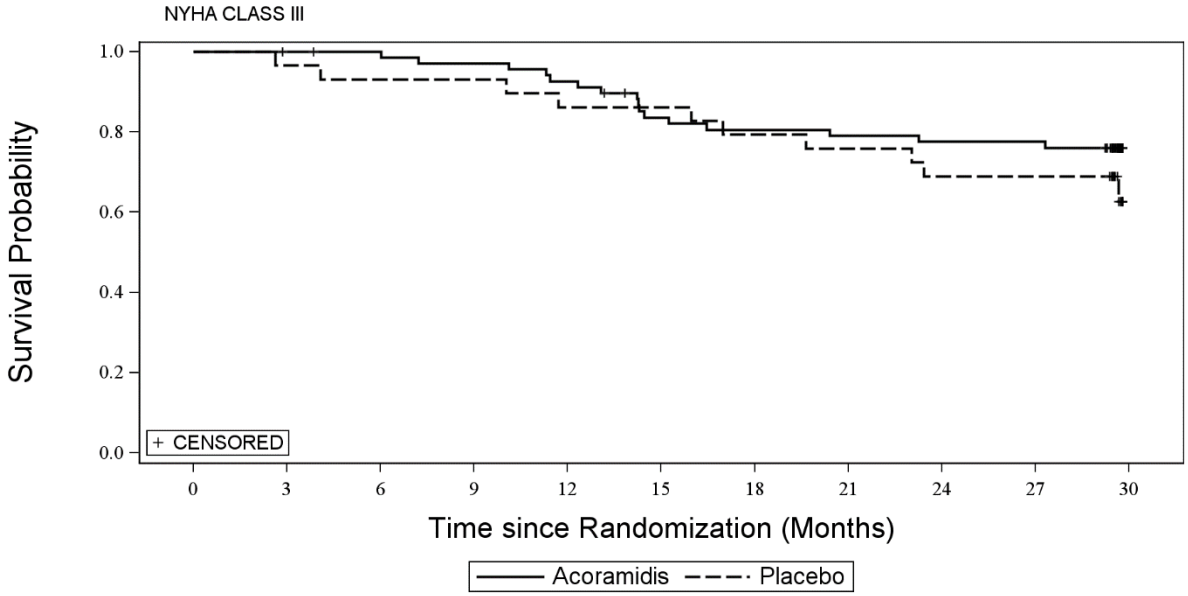
Figure 15: Kaplan-Meier Curve for Time to All-Cause Mortality Over month 30 in NYHA Class III, mITT Population



Abbreviations: mITT = modified intent-to-treat; NYHA = New York Heart Association
Note: All-cause mortality is including all cause death, heart transplant and Cardiac Mechanical Assist Device Implantation

Source: Day 120 Response, Figure 14.4.1.16

Figure 16: Kaplan-Meier Curve for Time to CV Mortality Over month 30 in NYHA Class III, mITT Population

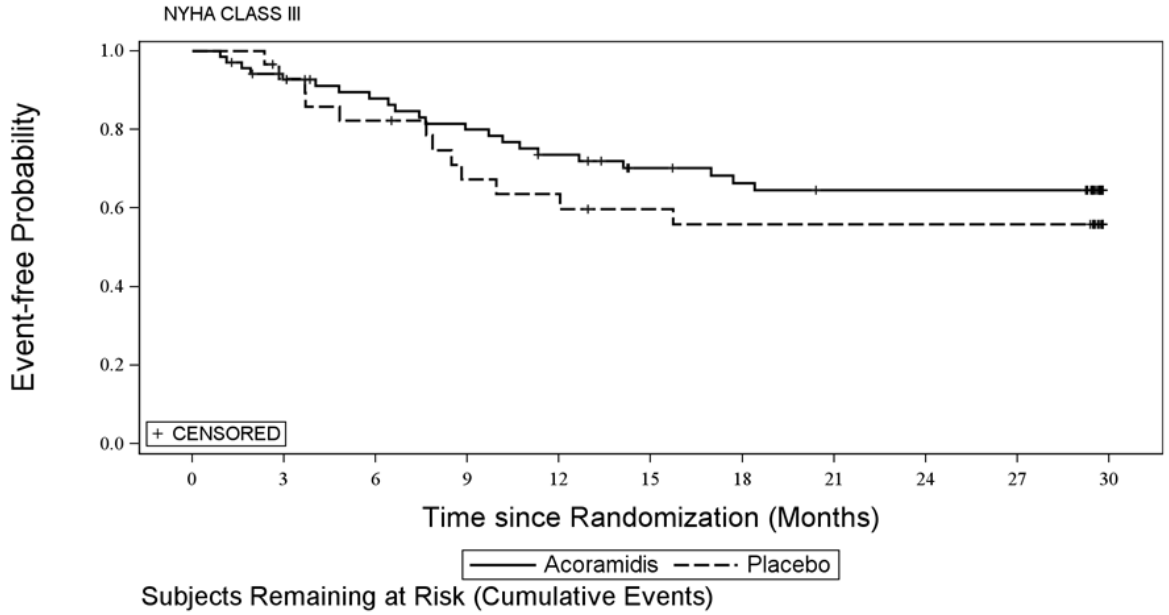


Subjects Remaining at Risk (Cumulative Events)

Acoramidis	70 (0)	69 (0)	68 (0)	66 (2)	63 (5)	55 (11)	53 (13)	52 (14)	51 (15)	51 (15)	0 (16)
Placebo	29 (0)	28 (1)	27 (2)	27 (2)	25 (4)	25 (4)	23 (6)	22 (7)	20 (9)	20 (9)	0 (10)

Abbreviations: CV = cardiovascular; mITT = modified intent-to-treat; NYHA = New York Heart Association
Source: Day 120 Response, Figure 14.4.1.17

Figure 17: Kaplan-Meier Curve for Time to First CV-Related Hospitalisation Over month 30 in NYHA Class III, mITT Population

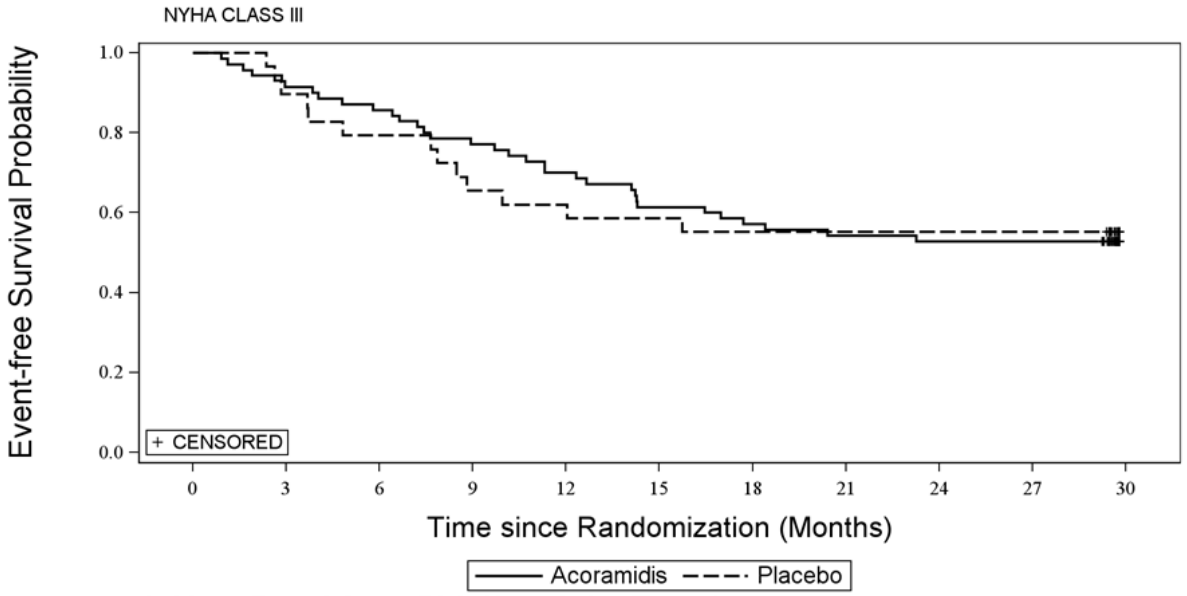


Subjects Remaining at Risk (Cumulative Events)

Acoramidis	70 (0)	62 (5)	55 (8)	50 (13)	45 (17)	38 (19)	35 (21)	33 (22)	33 (22)	33 (22)	0 (22)
Placebo	29 (0)	26 (2)	23 (5)	18 (9)	17 (10)	15 (11)	14 (12)	14 (12)	14 (12)	14 (12)	0 (12)

Abbreviations: CV = cardiovascular; mITT = modified intent-to-treat; NYHA = New York Heart Association
Source: Day 120 Response, Figure 14.4.1.18

Figure 18: Kaplan-Meier Curve for Time to All-Cause Mortality or First CV-Related Hospitalisation Over month 30 in NYHA Class III, mITT Population



Subjects Remaining at Risk (Cumulative Events)

Acoramidis	70 (0)	64 (6)	60 (10)	54 (16)	49 (21)	43 (27)	40 (30)	38 (32)	37 (33)	37 (33)	0 (33)
Placebo	29 (0)	26 (3)	23 (6)	19 (10)	18 (11)	17 (12)	16 (13)	16 (13)	16 (13)	16 (13)	0 (13)

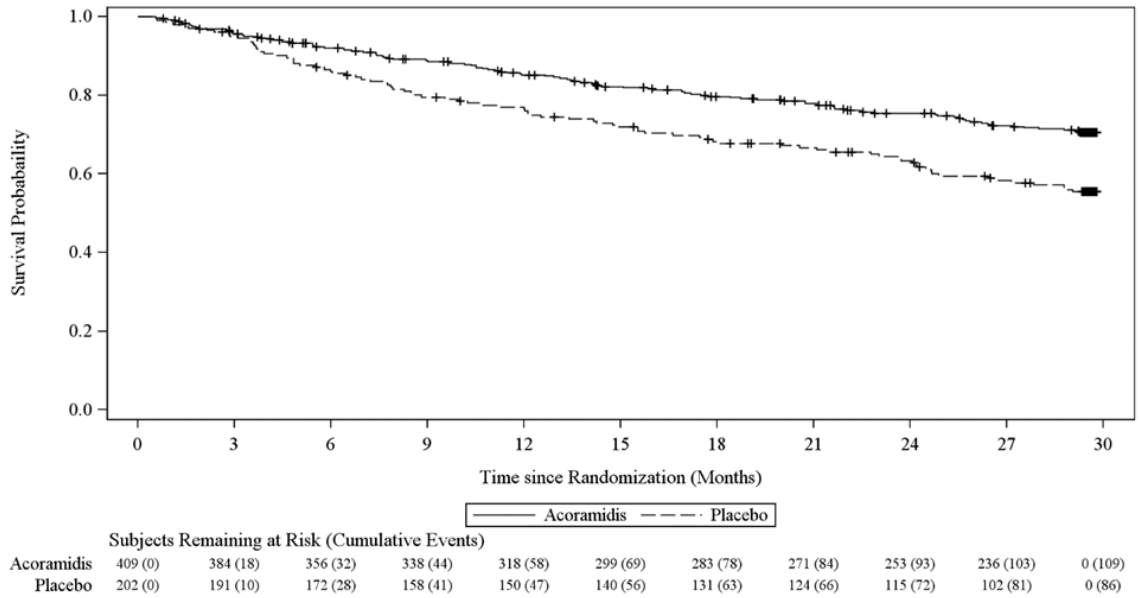
Abbreviations: CV = cardiovascular; mITT = modified intent-to-treat; NYHA = New York Heart Association
Source: Day 120 Response, Figure 14.4.1.27

From the presented data, it is clear that in the studied population, those with worse cardiac function performed globally worse in response to treatment with acoramidis. This was consistent across all studied endpoints in both mITT and ITT population, in line with the expected mode of action and similar to what is known for tafamidis. Although the lack of study power for the NYHA class III population, this robust consistency clearly requires signalling of this population as lower benefiters. Similar to already approved amyloid stabiliser agent, this lower efficacy signal has been requested to be clearly stated in section 5.2 of SmPC. Likewise, it was requested that the response of NYHA Class III patients and NAC ATTR stage is clearly identified as compared to the other classes.

CV-related Hospitalisation

Acoramidis delayed the first occurrence of CV-related hospitalisation in comparison to placebo. The Kaplan-Meier curves for time to CV-related hospitalisation show a separation, starting early at month 3, and increasing in magnitude through month 30. A clinically relevant treatment effect was observed for acoramidis compared to placebo (hazard ratio: 0.601, stratified Cox proportional hazard model; 95% CI: 0.451, 0.800; nominal p value = 0.0005).

Figure 19: Kaplan-Meier Curve for Time to First CV-related Hospitalisation Over month 30, mITT Population



Abbreviation: CV = cardiovascular; mITT = modified intent-to-treat

A statistically significant / clinically important 50.4% relative risk reduction was observed for acoramidis compared to placebo on the annualised frequency of CV-related hospitalisation (imputed: acoramidis: 0.224, placebo: 0.450; relative risk ratio = 0.496; nominal $p < 0.0001$).

Acoramidis delayed the first occurrence of CV-related hospitalisation in comparison to placebo. The Kaplan-Meier curves for time to CV-related hospitalisation show a separation, starting early at month 3, and increasing in magnitude through month 30 (Figure 19, hazard ratio 0.601; stratified Cox proportional hazard model; 95% CI: 0.451, 0.800; nominal p value = 0.0005).

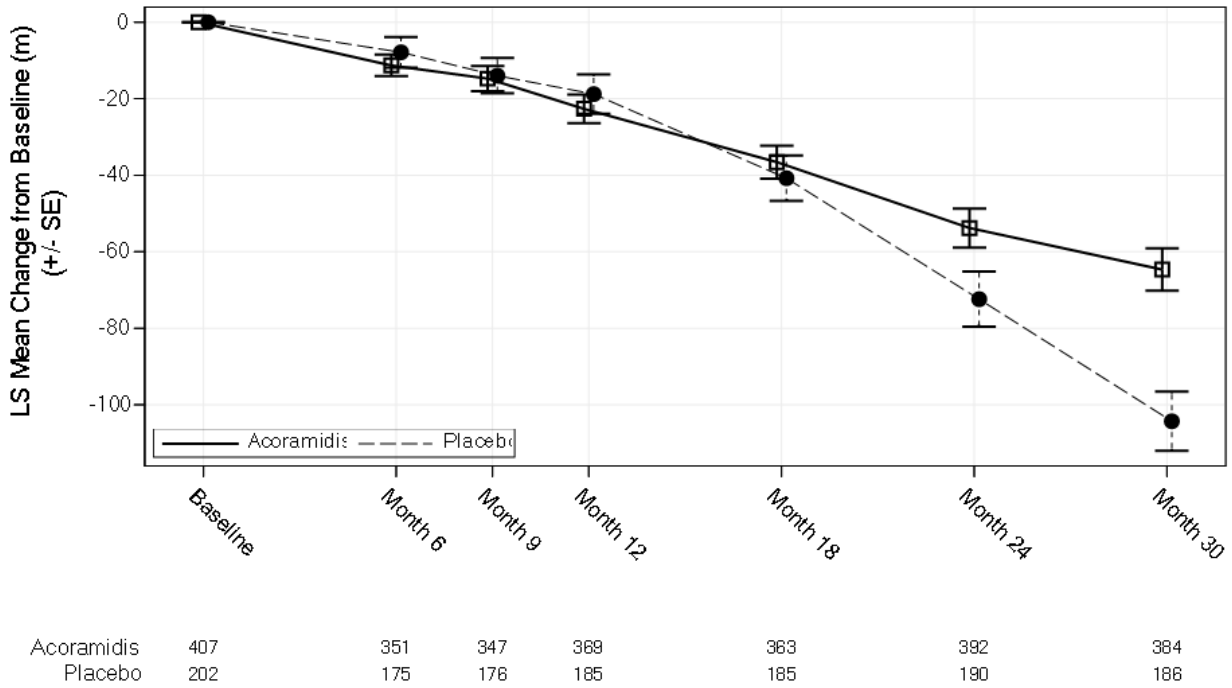
It is interesting to note that time to first hospitalisation appeared to show an effect quite early within 3 months, which is not in line with what has been expected from tafamidis, where the curves for Time to First Cardiovascular Hospitalisation started to separate not before month 9 (Maurer et al. 2018, Supplementary Figure S1). As this does not raise concerns, the issue does not have to be further discussed.

The main analysis results on CV-related hospitalisation were robust when applying the Hypothetical Strategy and the Principal Stratum Strategy (supplementary analyses to assess the potential effects of concomitant tafamidis). A statistically significant consistent result (nominal $p \leq 0.0005$) was observed using both strategies.

6MWD (Functional Outcome)

A treatment effect for change from baseline in 6MWD favouring acoramidis was observed, with the curves starting to separate at month 18, and with separation increasing in magnitude through month 30. This separation starting at month 18 illustrates why significance in 6MWD was not achieved at month 12 in Part A of the study.

Figure 20: Least Squares Mean (± SE) Change from Baseline in 6MWD (Meters) Over Time (with J2R), mITT Population



Acoramidis	407	351	347	369	363	392	384
Placebo	202	175	176	185	185	190	186

Abbreviations: 6MWD = 6-minute walk distance; ATTRv-CM = variant transthyretin amyloidosis cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloidosis cardiomyopathy; eGFR = estimated glomerular filtration rate; J2R = Jump to Reference; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SE = standard error
Notes: The change from baseline in 6MWD was analysed using the MMRM with treatment group, visit, genotype (ATTRv-CM versus ATTRwt-CM), NT-proBNP level (≤ 3000 versus > 3000 pg/mL), eGFR level (≥ 45 versus < 45 mL/min/1.73 m^2) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study drug were imputed using the J2R method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values. Ns represent both observed and imputed data points.

At month 30, a statistically significant ($p < 0.0001$) and clinically meaningful treatment effect on 6MWD was observed favouring acoramidis, with 40 meters LS mean difference between treatment groups in change from baseline. At month 30, the observed means of 6MWD were 366 meters and 322 meters in the acoramidis and placebo groups, respectively. The observed mean (percent) changes from baseline in 6MWD at month 30 were -23 meters (-5.7%) and -50 meters (-14.3%) in the acoramidis and placebo groups, respectively. In a post-hoc analysis with imputation (that accounted for missing observations), at month 30, a net increase in 6MWD relative to baseline, an indication of clinical improvement, was observed in 26.2% of participants in the acoramidis treatment group, compared to 13.4% in the placebo group (nominal $p = 0.0002$.

The sensitivity analyses showed consistent results and, therefore, demonstrated the robustness of the 6MWD results. The results of the two supplementary analyses, conducted to address the potential effect of concomitant tafamidis use, were consistent with the primary analysis results of 6MWD in the mITT Population. A favourable treatment effect of acoramidis over placebo on 6MWD was still observed after controlling for the potential effect of concomitant tafamidis use.

The time course with a late effect of acoramidis on 6-MWD is in contrast to the results with tafamidis (Maurer et al., 2018) where an effect on 6 MWD was seen quite early starting within the first 6 months of treatment. Considering the same mechanism of action, the difference is not quite well understood. Of note, it is understood that the treatment effect was only seen late during the study after the negative results for 6-MWD became available from part A. Ceiling effects in high performers at baseline

may have to be considered. The applicant was asked to provide analyses for the 6MWD differentiating by baseline performance.

The applicant provided data on 6-MWD for patients in the upper quartile of baseline performance. Change from baseline was around 30 m (median)/26 m (median) better in the treatment arm indicating the absence of a relevant ceiling effect in these patients.

Table 15: Summary and Change from Baseline n Distance Walked (m) during 6MWT at Baseline and Month 30 (for participants with baseline 6MWD within upper quartile range in each treatment arm), mITT population

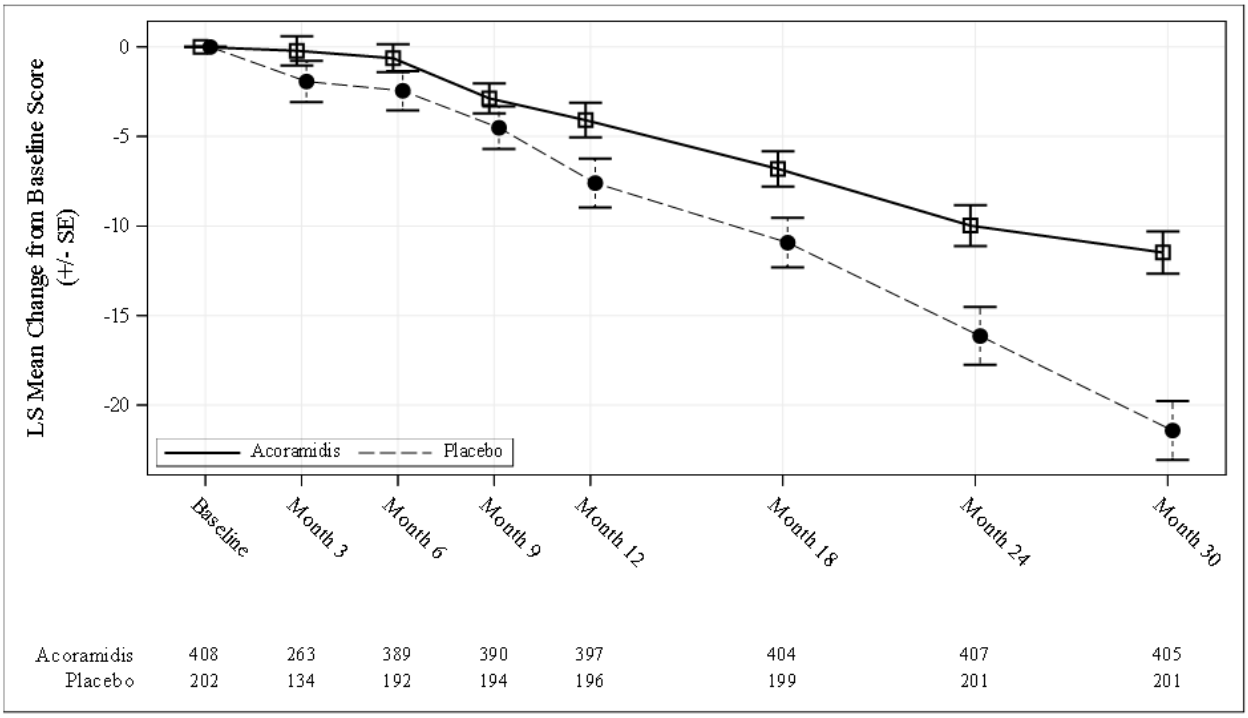
Distance Walked (m)	Acoramidis (N = 102)	Placebo (N = 51)
Baseline		
Observed Value		
n	102	51
Mean (SD)	495.15 (58.757)	470.06 (42.394)
Median (Q1, Q3)	477.14 (450.60, 518.68)	461.55 (437.87, 495.50)
Min, Max	435.0, 695.8	409.8, 598.4
Month 30		
Observed Value		
n	90	37
Mean (SD)	466.62 (112.502)	411.14 (100.588)
Median (Q1, Q3)	480.56 (385.60, 528.96)	435.75 (372.28, 463.10)
Min, Max	78.5, 703.4	105.0, 590.1
Change from Baseline		
n	90	37
Mean (SD)	-33.06 (91.529)	-62.95 (84.631)
Median (Q1, Q3)	-14.65 (-78.95, 31.20)	-41.15 (-112.50, -10.51)
Min, Max	-406.1, 165.8	-304.8, 58.9

Abbreviations: 6MWD = Six-Minute Walk Distance; distance achieved in a standardized 6MWT; 6MWT = Six-Minute Walk Test; Max = maximum; min = minimum; mITT = modified intent-to-treat; Q = quarter; SD = standard deviation.
Source: Day 120 Response, Table 14.4.1.141

KCCQ-OS Quality of Life

A treatment effect for change from baseline in KCCQ-OS favouring acoramidis was observed early, with the curves starting to separate at month 3, and separation increasing in magnitude through month 30.

Figure 21: Least Squares Mean (± SE) Change from Baseline in KCCQ-OS over Time (with J2R), mITT Population



Abbreviations: ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt CM = wild-type transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; J2R = Jump to Reference; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; SE = standard error
Notes: The change from baseline in KCCQ-OS was analysed using the MMRM with treatment group, visit, genotype (ATTRv-CM versus ATTRwt-CM), NT-proBNP level (≤ 3000 versus > 3000 pg/mL), eGFR level (≥ 45 versus < 45 mL/min/1.73 m^2) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study drug were imputed using the J2R method. Missing measurements due to death were performed by sampling with replacement from the worst 5% of observed values. Ns represent both observed and imputed data points.

At month 30, a statistically significant ($p < 0.0001$) treatment benefit on the KCCQ-OS, was observed favouring acoramidis, with a 10-point increase from baseline LS mean difference observed between the two treatment groups. An improvement in KCCQ-OS with acoramidis, relative to placebo, was observed, numerically, across all KCCQ-domains. The impact of acoramidis on health status and QoL, as demonstrated in the KCCQ-OS, underscores the clinically meaningfulness of the 6MWD treatment effect.

Table 16: Analysis of Change from Baseline in KCCQ-OS at month 30– MMRM (with J2R), mITT Population

	Acoramidis (N = 409)	Placebo (N = 202)
month 30		
Change from Baseline		
n	405	201
LS Mean	-11.48	-21.42
SE	1.181	1.651
95% CI	-13.79, -9.16	-24.66, -18.18
96% CI	-13.90, -9.05	-24.81, -18.03
LS Mean Difference Active Dose - Placebo	9.94	

	Acoramidis (N = 409)	Placebo (N = 202)
SE for Difference	2.024	
95% CI for Difference	5.97, 13.91	
96% CI for Difference	5.79, 14.10	
p value	< 0.0001	

Abbreviations: CI = confidence interval; J2R = Jump to Reference; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS = least squares; MMRM = mixed model for repeated measures; mITT = modified intent-to-treat; Q = quartile; SE = standard error

At month 30, the observed mean KCCQ-OS scores were 71 and 64 in the acoramidis and placebo groups, respectively. The observed mean (percent) changes from baseline in KCCQ-OS score at month 30 were -3.1 (-3.0%) and -10.8 (-14.0%) in the acoramidis and placebo groups, respectively.

In a post-hoc analysis with imputation (that accounted for missing observations), at month 30, a net increase in KCCQ-OS relative to baseline was observed in 30.8% of participants in the acoramidis treatment group, compared to 17.8% in the placebo group (nominal p = 0.0005).

For the KCCQ thresholds of 5 and 10 points of change, representing respectively small and moderate improvement from the clinician perspective, have been accepted as being clinically relevant. In this respect the result of a LS Mean Difference Active Dose – Placebo of 9.94 (95% CI for Difference5.97, 13.91) indicates a moderate (at least small) improvement.

Furthermore, the applicant provided a discussion for the time from treatment initiation to a clinically relevant effect. The earliest clinically relevant effect favouring acoramidis over placebo was reported in CV-related hospitalisation at month 3, with the effect on all-cause mortality reported later at month 19. A possible biological justification based upon amyloid stabilisation and amyloid burden was provided, in line with the expected mechanism of action of acoramidis, which is acceptable.

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17: Summary of efficacy for trial

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)		
Study identifier	AG10-301	
	EU CT number	2018-004280-32
	NCT number	NCT03860935 (not provided)
	ISRCT number	not provided
	Other identifier(s)	IND Number: 133574
Design	A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 (800 mg bid acoramidis) in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)	
	Duration of main phase:	30 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	Ongoing, a separate study (AG10-304)
Hypothesis	Superiority	
Treatments groups	Acoramidis (Acor)	Acoramidis 800mg bid, 30 months duration, 409 pts

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)			
Study identifier	AG10-301		
	EU CT number	2018-004280-32	
	NCT number	NCT03860935 (not provided)	
	ISRCT number	not provided	
	Other identifier(s)	IND Number: 133574	
	Placebo (Pbo)		Placebo bid, 30 mths duration, 202 patients
Endpoints and definitions	Primary endpoint	ACM+CVH+6MWD+NT-proBNP F-S test	Hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalisation, change from baseline in NT-proBNP, and change from baseline in 6MWD over the 30-month treatment duration; was analysed by the Finkelstein-Schoenfeld (F-S) method.
	Secondary endpoint	6MWD	Change from baseline to month 30 of treatment in 6MWD
	Secondary endpoint	KCCQ-OS	Change from baseline to month 30 of treatment in KCCQ Overall Summary Score (KCCQ-OS).
	Secondary endpoint	ACM	All-cause mortality by month 30, including death due to any cause, heart transplant, or CMAD
Database lock	06 July 2023		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat 30 month		
Descriptive statistics and estimate variability	Treatment group	Acor	Pbo
	Number of subject	409	202
	ACM+CVH+6MWD+NT-proBNP F-S test Wins	18346	10351
	6MWD Least Squares Mean	- 22.73	-49.98
	SD	79.355	83.578
	KCCQ-OS Least Squares Mean	-3.12	-10.81
	SD	16.977	19.434
	ACM cumulative	79	52
Effect estimate per comparison	Primary endpoint	Comparison groups	Acor vs. Pbo
		FS Win ratio	1.772
		96% CI of Win Ratio	(1.402-2.240)
		p value from F-S test	< 0.0001
	Secondary endpoint 6MWD	Comparison groups	Acor vs Pbo
		Difference between groups	39.64
		96% CI for difference	20.18, 59.10
		P-value	<0.0001
	Secondary endpoint KCCQ-OS	Comparison groups	Acor vs Pbo
		Difference between groups	9.94

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)			
Study identifier	AG10-301		
	EU CT number	2018-004280-32	
	NCT number	NCT03860935 (not provided)	
	ISRCT number	not provided	
	Other identifier(s)	IND Number: 133574	
		96% CI for difference	5.79, 14.10
		P-value	<0.0001
	Secondary endpoint ACM	Comparison groups	Acor vs Pbo
		Cox Proportional Hazard Model Hazard Ratio (versus Placebo)	0.772
		96% CI of Hazard Ratio	0.532, 1.121
		P-value	0.1543
Notes			

2.6.5.3. Clinical studies in special populations

Table 18: Summary Table of Baseline Renal Impairment, Hepatic Impairment and Age, Safety Population

Participant Characteristic	Number of Participants/Total Number	
	Controlled Trials[c] (N = 681) n/N (%)	Non-controlled Trials[d] (N = 436) n/N (%)
Renal impairment[a] participants	146/681 (21.4%)	140/436 (32.1%)
Hepatic impairment[b] participants	2/681 (0.3%)	1/436 (0.2%)
Paediatric participants < 18 years	0/681	0/436
Participants age 65-74 years	217/681 (31.9%)	105/436 (24.1%)
Participants age 75-84 years	370/681 (54.3%)	235/436 (53.9%)
Participants age 85+ years	71/681 (10.4%)	84/436 (19.3%)
Other (age 18-64 years)	23/681 (3.4%)	12/436 (2.8%)

[a] Renal impairment is defined as having eGFR< 45 mL/min/1.73 m^2.
[b] Hepatic impairment is defined as ALT or AST > 3 x ULN.
[c] Controlled Trials include Study AG10-201 and Study AG10-301. Baseline assessments from Study AG10-201 and Study AG10-301 were used for analysis.
[d] Non-controlled Trials include ongoing Study AG10-202 and Study AG10-304. Study AG10-202 is the open-label extension study of Study AG10-201. Study AG10-304 is the open-label extension study of Study AG10-301. All participants enrolled in Study AG10-202 and Study AG10-304 have participated in the respective preceding Study AG10-201 and Study AG10-301. Baseline assessments from Study AG10-202 and Study AG10-304 were used for analysis. Data cutoff dates of 09 October 2023.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.6. Discussion on clinical efficacy

Dose finding

The dose administered in the Phase 3 studies was acoramidis HCl 800 mg BID, administered as two 400 mg tablets, each equivalent to 356 mg acoramidis (total dose of 712 mg acoramidis [active moiety]).

The rationale to select a higher 800 mg BID over the 400 mg BID dose in the phase 3 study was mainly based on study AG10-210 and an expected higher efficacy with respect to increases in serum TTR levels, TTR stabilisation and on acoramidis trough levels. Dose response of efficacy was further analysed in the PopPK/PD analysis EIDO-PMX-AG10-2264 (based on data from Study AG10-201 final data set, interim data from Study AG10-202, and from Study AG10-301 final data sets) indicating a positive correlation between acoramidis exposure (AUCss) and increased serum TTR relative to baseline at month 30. An increased exposure was associated with a decreased number of expected cardiovascular hospitalisations. The model indicated a small, positive relationship between increasing serum TTR by day 28 of treatment and increased CfB in 6MWT at month 30. In the final exposure-

response model increased acoramidis concentrations were associated with decreases in %CfB NT-proBNP concentrations at month 30 of treatment. In the time to event models for all cause mortality the base model indicated decreasing hazard and thus increased survival probability with increasing serum TTR at day 28.

Only limited data are available on comparative safety between 400 mg BID and 800 mg BID. These data reasonably indicate a dose response within the investigated dose range. Regarding efficacy the choice of the dose 800 mg over a 400 mg BID dose can be followed.

Design and conduct of clinical studies

The key study to support efficacy was the ATTRibute-CM Trial (Study AG10-301), A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy. It was a prospective, Phase 3, randomised, multicentre (117 centres worldwide, 95 centres randomised patients), parallel-group study to evaluate the efficacy and safety of acoramidis (712 mg twice daily bid, equivalent to acoramidis HCl 800 mg bid) in symptomatic patients compared to placebo, on a background of stable heart failure therapy. Screening and randomisation were followed by a total of 30 months of blinded, placebo-controlled treatment. Results at the end of the total 30 months of treatment were presented.

It was planned to include approximately 510 male and female participants ≥ 18 and ≤ 90 years of age with chronic, stable, symptomatic (NYHA Class I-III) ATTR-CM, randomised in a 2:1 ratio (acoramidis: placebo). Participants were stratified at randomisation based on whether they had wild-type ATTR-CM (ATTRwt-CM) or mutant ATTR-CM (ATTRm-CM, hereafter referred to as variant ATTR-CM [ATTRv-CM]) with a target of 20% of participants with ATTRv-CM. Participants were also stratified according to NT-proBNP level (≤ 3000 versus > 3000 pg/mL) and renal function defined by eGFR (≥ 45 versus < 45 mL/min/1.73 m^2) at Screening.

In principle, a single pivotal trial can be acceptable for a rare disorder. The choice of placebo as comparator could be acceptable in local sites where tafamidis was not accessible, particularly when it became on label for both ATTRv and ATTRwt symptomatic cardiomyopathy.

The study employed an embedded study design consisting of a 12-month functional readout (Part A) and a 30-month mortality, morbidity, and functional readout (Part B), each with different primary endpoints. The total α spend of 0.05 was allocated as 0.01 for Part A and 0.04 for Part B.

At the end of 12 months of treatment (Part A), the efficacy of acoramidis was assessed by analyses of the primary functional (6MWD) and key secondary health-related QoL (KCCQ-OS) endpoints. The Part A readout did not meet its primary endpoint and the study continued as planned.

Primary efficacy Endpoint:

The primary endpoint was subject to change during the study. At the time of closure of SAP it was:

a) A hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalisation, change from baseline in NT-proBNP, and change from baseline in 6MWD over the 30-month fixed treatment duration.

Key Secondary Endpoints:

b) Change from baseline to month 30 of treatment in 6MWD.

c) Change from baseline to month 30 of treatment in KCCQ Overall Summary Score (KCCQ-OS).

d) Change from baseline to month 30 in serum TTR level (an in vivo measure of TTR stabilisation).

e) All-cause mortality by month 30, including death due to any cause, heart transplant, or CMAD.

Other Secondary Endpoints:

f) A hierarchical combination of all-cause mortality and cumulative frequency of CV-related hospitalisation over a 30-month fixed treatment duration.

g) A hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalisation, and change from baseline in 6MWD over a 30-month fixed treatment duration.

h) CV-mortality by month 30.

i) Cumulative frequency of CV-related hospitalisation by month 30.

j) Change from baseline in TTR level at month 30 and TTR stabilisation measured in established ex vivo assays (Fluorescent Probe Exclusion [FPE] and Western blot [WB]) in the PK-PD substudy.

k) Change in NT-proBNP from baseline to month 30 of treatment.

The eligibility criteria are adequate. The criterion of “NYHA Class I-III symptoms due to ATTR-CM” needed further explanation since patients at NYHA I are usually considered asymptomatic at rest or at regular exercise. The applicant commented on present / past symptoms documented in patients with NYHA I. It was not clearly stated in the Product Information that all patients had symptomatic disease or a history of symptomatic disease at the time of randomisation as suggested by the inclusion criterion „NYHA Class I-III symptoms due to ATTR-CM“. The applicant upon request reflected this in section 5.1 of the SmPC. It was also highlighted in section 5.1 of the SmPC that a lower response of NYHA Class III patients is observed as compared to the other classes.

No upper limit was predefined for the 6-MWT which might lead to ceiling effects in good performers at baseline. Evaluations for the results on the 6-MWT by baseline performance however, have shown that the results have not been jeopardised.

NT-proBNP levels ≥ 300 pg/mL at screening did not differentiate between whether patients had atrial fibrillation (57.8%) or not. It may be relevant for the analyses of change in NT-proBNP as an efficacy parameter. The applicant provided efficacy results for NT-proBNP in the pivotal study, differentiating between patients with/without atrial fibrillation at baseline including analyses of the impact of persistent vs. paroxysmal atrial fibrillation and for those patients that developed atrial fibrillation de novo during the study. As expected, AF influenced NT-proBNP levels, but the effect was similar in both treatment arms. Numerical data (time to AF, NT-proBNP levels) favoured the acoramidis arm.

Tafamidis was not allowed during the first year of treatment over the first year, patisiran (within 90 days) and inotersen (within 180 days) were also not allowed. Albeit understandable for the demonstration of efficacy, treatments not allowed during the study were asked to be appropriately reflected in the SmPC. This is especially relevant for non wt forms where other organ amyloidopathy is expected.

On the SAP:

Protocol deviations were balanced but rather high with 46.0% of “Any Important Protocol Deviation”, 20.0% related to inclusion criteria and 17.7% to informed consent. There were no centre or country

clusters, and most protocol deviations were related to procedural and logistical aspects, none raised ethical suspicions.

Several amendments were made on the definition of the primary and secondary endpoints while the study was ongoing. Amendment 5 included 6-MWD as an additional component, Amendment 6 change from baseline in NT-proBNP as an additional component to be analysed in the hierarchical testing procedure. These changes were clearly discouraged during CHMP protocol assistance procedures. An additional change on diuretic use as proposed in the definition of CV-endpoint events also discouraged during a scientific advice procedure was not implemented.

The finally implemented primary endpoint was not acceptable. The initially defined endpoint (all-cause mortality [ACM] and CV hospitalisations [CVH] including recurrent events) and the additional analysis of a first event analysis of all-cause mortality and CV hospitalisation were provided upon response to the major objection (MO) raised in the first round of the assessment. Additional analyses for the dual endpoints were provided in order to further analyse the robustness.

The randomisation was not stratified by region or centre. The applicant has provided subgroup analyses for “US (~20%) vs Rest of the World (~80%)” but not for the EU separately. A subgroup analysis for the EU was provided: 355 out of 611 patients were recruited in the EU. Significance was not achieved for the 2-step hierarchical analysis of ACM and CVH in the EU sites but this is not unexpected. The results were overall consistent for the primary and key secondary analyses in the EU as compared to the overall population. The results on efficacy are relevant for the EU population.

The mITT population was the primary analysis population for efficacy endpoints and included participants who met the definition of ITT and had a baseline eGFR ≥ 30 mL/min/1.73 m^2. The rationale of excluding patients with eGFR < 30 mL/min/1.73 m^2 from the primary efficacy analyses is unclear and should be explained. For the ITT population, only analyses of all-cause mortality and CV mortality were included in the clinical study report (CSR). Analyses of other relevant primary and secondary endpoints in the ITT population and in the subgroup of patients with a baseline eGFR < 30 mL/min/1.73 m^2 were provided.

From the CSR it is understood that the vital status could be collected for all patients, so that all pairwise comparisons with regard to all-cause mortality were performed at month 30. Nevertheless, for the other components (CVH, NT-proBNP, 6MWD) measurements after premature study discontinuation prior to month 30 were missing and the missing values were not imputed in the primary analysis, leading to pairwise comparisons with regard to the non-fatal components at various different timepoints in the primary analysis. The clinical plausibility and relevance of this analysis were questionable because comparisons were not conducted at a unified relevant timepoint; furthermore, the measurements after premature study discontinuation (this also implies premature treatment discontinuation) may follow a different distribution as the measurements on treatment. To mitigate this, an analysis for the estimand truly using the treatment policy strategy for all intercurrent events with an appropriate imputation of missing data after premature study discontinuation was conducted.

The applicant has conducted several sensitivity analyses of the primary endpoint to examine the impact of missing data on the interpretation of results.

An overview of mis-stratifications was presented.

The comparison was made to the study with tafamidis in patients with ATTR cardiomyopathy and to the response of patients with added tafamidis after month 12 of treatment with acoramidis. The results do not allow to conclude that acoramidis is more efficient than tafamidis. Tafamidis study was performed when diagnosis of ATTR cardiomyopathy was much more invasive, and less information on the management of these patients was known, and therefore the comparison is heavily biased. Addition of tafamidis during the AG10-301 trial was not randomised, and many patients withdrew from

the study to take it before month 12.

Efficacy data and additional analyses

The study population was representative of the overall population with ATTR-CM. Overall, the mean age at randomisation was 77 years and almost all participants (96.6%) were≥ 65 years-of-age. Most participants were male (90.8%), White (87.9%), recently diagnosed with ATTR-CM (mean 1.2 years, range 0-10.1 years), and within NYHA Class II (72.7%). Ninety-nine participants (16.2%) were within NYHA Class III. Twenty-nine participants (4.7%) were Black. No notable imbalances were observed between the treatment groups by stratification factors. Fifty-six participants (9.2% of mITT Population) had ATTRv-CM, and 62.5% of these 56 participants were V122I. Overall, four participants were homozygotes for the TTR mutation (all V122I). Most participants, 75.9%, were diagnosed non-invasively without endomyocardial biopsy. These baseline ATTR-CM characteristics were generally well balanced between the treatment groups. Overall, 57.8% of participants had atrial fibrillation, 18.8% had a permanent pacemaker placed, and 43.4% had prior carpal tunnel release surgery. These baseline ATTR-CM history characteristics were generally well balanced between the treatment groups.

The number of participants who initiated tafamidis at any point during the study (i.e., before or after the month 12 visit) was greater in the placebo group compared to the acoramidis treatment group (22.8% versus 14.9%). Overall, the median time to initiation of tafamidis (relative to randomisation) and median duration of exposure to tafamidis during the study were 17.22 and 11.40 months, respectively, and was comparable between the two treatment groups.

No information was available on patients with end stage cardiac disease at study entry. Some exploratory information was requested to be collected from patients progressing to end stage disease (NYHA IV) during the course of the study. The applicant provided this information.

The primary endpoint was met and showed a statistically significant positive treatment effect of acoramidis relative to placebo ($p < 0.0001$). The win ratio for the primary analysis was 1.772 (96% CI: 1.402, 2.240).

While the F-S test has been used to characterise the efficacy of cardiovascular medication, a major concern is that the applicant has changed the primary endpoint when all patients had been enrolled into the study, against EMA advice. As such, the primary endpoint is not accepted as key evidence to support efficacy as described above. Neither NT-proBNP nor a win ratio for 6-MWD are accepted as components. The result is to a large degree driven by the cumulative frequency of CV-related hospitalisation and even more by the difference in NT-proBNP.

The main outcome most relevant for the assessment are the following two endpoints:

1) The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period (primary endpoint as initially defined before amendments 5 and 6). Numerically, statistical significance was achieved on the two-component (all-cause mortality and frequency of CV-related hospitalisations) F-S test, which demonstrated the superior treatment effect of acoramidis compared to placebo (nominal p = 0.0182

2) Time to All-cause Mortality or First CV-related Hospitalisation. The Kaplan-Meier curves for time to all-cause mortality or first CV-related hospitalisation started to separate at month 3 and this effect was sustained through to month 30. The composite of time-to-first-event of all-cause mortality or CV-related hospitalisation was reported in 147 (35.9%) and 102 (50.5%) acoramidis and placebo-treated participants, respectively, corresponding to a 14.6% absolute risk reduction. A 35.5% hazard reduction in all-cause mortality or first CV-related hospitalisation at month 30 was observed in the acoramidis treatment group compared to placebo (hazard ratio: 0.645 [95% CI: 0.500, 0.832; nominal p = 0.0008]. The difference was mainly driven by first CV hospitalisations.

The applicant was requested to provide the results for the ITT populations for the following endpoints:

- The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period
- Time to All-cause Mortality or First CV-related Hospitalisation
- CV related hospitalisation

The hierarchical order of the (Key) secondary endpoints is not understood. Change from baseline to month 30 of serum TTR level is ranked 3rd, and should be last, whilst All-Cause Mortality by month 30 (stratified cox proportional hazard model) which is ranked 4th should be ranked first in terms of clinical or patient relevance.

There has been a high number of enrolment failures, including withdraw of consents and “other reasons”. Since in some local sites tafamidis was already available and patients were not allowed to take it in the first year of the trial. The applicant provided a discussion on the aspect, in particular in the subgroups of other reasons and withdrawn consents. The previous concern that the enrolled population might have been recruited from the less favoured does not seem to be supported by the presented data. Most screen failures were due to the narrow time window for inclusion and other procedural aspects, and due to COVID 19 restrictions. A very small number of patients may have failed inclusion in relation to tafamidis access (1 to pursue tafamidis and 7 where tafamidis was already available at inclusion) which is less than 4% of the screening failures, and this is not expected to have impacted in the results.

Subgroup analyses

The applicant has provided subgroup analyses for the primary efficacy endpoint and for secondary efficacy endpoints including 6 MWD, All-cause mortality, and cumulative rate of CV hospitalisations.

Overall, the results were consistent for most subgroups with the exception of NYHA class III. For the primary 4-fold efficacy endpoint and for the 6-MWD, HRs did not indicate efficacy in patients with NYHA III and only little efficacy was observed for the cumulative frequency of CV hospitalisations.

For all-cause mortality, the point estimate of the HRs was even in favour of placebo seemingly with an early shift favouring placebo around month 12 which is reversed by month 19. The latter finding was discussed further since Table 14.2.1.81 of the study report provided a lower rate of deaths with acoramidis in patients with NYHA III. It was further explained by the applicant and Kaplan - Meier curves for mortality by NYHA category were provided. Considering that also data available for tafamidis indicated a lower efficacy in patients with NYHA III (Maurer et al., 2018) the results may indeed indicate a lower efficacy in advanced stages of the disease. The consistent result of a lower/absent efficacy in patients at NYHA III was further discussed and analysed. The efficacy in these patients was not considered established and a major objection was raised in the first round of the assessment. In order to better understand the observation analyses by subgroups NYHA III vs. NYHA II vs. NYHA I and by NAC ATTR Stage III vs. II vs. I were requested for the following outcomes both for the ITT and the mITT population:

- The hierarchical combination of all-cause mortality and CV-related hospitalisation over a 30-month period
- All-cause Mortality or First CV-related Hospitalisation.
- All-cause Mortality
- CV mortality

- First CV-related Hospitalisation.
- Cumulative Frequency of CV-related Hospitalisations (including recurrent events)
- 6-MWD

The applicant has provided the requested analyses by NYHA stage and NAC ATTR stage for key efficacy endpoints in the mITT and the ITT population. It is acknowledged that analyses should be interpreted with caution due to lower numbers of patients per subgroup and some numerical imbalances (e.g., sex and rate of patients with ATTRm-CM). However, the data consistently indicate lower efficacy in patients at NYHA stage III and NAC ATTR stage III as compared to patients at earlier stages or the disease. For example, there was no benefit for ACM or First CVH. A continuous trend to lower efficacy was consistent when comparing NYHA I over II to III. For NAC ATTR Stage, Stage I and II showed comparable results and only results in stage III indicated lower/absent efficacy. The numerically low /absent efficacy in morbidity/mortality related events, was accompanied by lower efficacy results both for 6-MWD and KCCQ-OS in NYHA III and NAC ATTR Stage III. Since patients were stratified according to NAC ATTR stage, this evaluation may possibly even provide more reliable data as compared to analyses by NYHA stage.

From the presented data, it is clear that in the studied population, those with worse cardiac function performed globally worse in response to treatment with acoramidis. This was consistent across all studied endpoints in both mITT and ITT population, in line with the expected mode of action and similar to what is known for tafamidis. Although the lack of study power for the NYHA class III population, this robust consistency clearly requires signalling of this population as lower benefiters. Similar to already approved amyloid stabiliser agent, this lower efficacy signal is described in section 5.2 of the SmPC.

Secondary endpoints of interest

Acoramidis delayed the first occurrence of CV-related hospitalisation in comparison to placebo. The Kaplan-Meier curves for time to CV-related hospitalisation show a separation, starting early at month 3, and increasing in magnitude through month 30 (hazard ratio 0.601; stratified Cox proportional hazard model; 95% CI: 0.451, 0.800; nominal p value = 0.0005).

A treatment effect for change from baseline in 6MWD favouring acoramidis was observed, with the curves starting to separate at month 18, and with separation increasing in magnitude through month 30. At month 30, a statistically significant ($p < 0.0001$) and treatment effect on 6MWD was observed favouring acoramidis, with 40 meters LS mean difference between treatment groups in change from baseline which represent a clinically meaningful difference. It is understood that the treatment effect was only seen late during the study after the negative results for 6-MWD became available from part A. Ceiling effects in high performers at baseline were considered, but this has not impacted the results.

A treatment effect for change from baseline in KCCQ-OS favouring acoramidis was observed early, with the curves starting to separate at month 3, and separation increasing in magnitude through month 30 (($p < 0.0001$). The result of an LS Mean Difference Active Dose – Placebo of 9.94 (95% CI for Difference5.97, 13.91) indicates a moderate (at least small) improvement.

2.6.7. Conclusions on the clinical efficacy

The concerns raised during the assessment of application regarding the demonstration of the clinical efficacy were resolved.

The applicant appropriately reflected in section 5.1 of the SmPC that all of patients had symptomatic disease at the time of randomisation, as suggested, by the inclusion criterion „NYHA Class I-III symptoms due to ATTR-CM“.

The lower efficacy signal in patients with NYHA III is now clearly stated in section 5.1 of the SmPC. The CHMP considered the application approvable from a clinical efficacy point of view.

2.6.8. Clinical safety

The evaluation of the safety of acoramidis is based on 12 clinical studies, including seven Phase 1 studies in healthy adult volunteers (Studies AG10-001, AG10-003, AG10-004, AG10-005, AG10-007, AG10-008 and ALXN2060-HV-101), two Phase 2 studies in patients with symptomatic ATTR-CM (double-blind Study AG10-201 and the ongoing OLE study to Study AG10-201 [Study AG10-202]), and three Phase 3 studies in patients with symptomatic ATTR-CM (pivotal Study AG10-301, ongoing OLE study to Study AG10-301 [Study AG10-304], and Study ALXN2060-TAC-302 conducted in Japan). In addition, an SAE narrative was provided for the single patient with ATTR-CM enrolled in the Phase 1 Expanded Access use study (Study AG10-999).

The dose administered in the Phase 3 studies was acoramidis HCl 800 mg BID, administered as two 400 mg tablets, each equivalent to 356 mg acoramidis (total dose of 712 mg acoramidis [active moiety]). This dose was selected to represent the optimal combination of potential efficacy, safety, and tolerability, based on nonclinical PK studies, data from the Phase 1, FIH, SAD, and MAD study (Study AG10-001), and the Phase 2, repeat dose, dose-ranging, safety, tolerability, PK and PD study (Study AG10-201). Participants who completed Phase 2 Study AG10-201 were invited to enrol in an OLE study (Study AG10-202); all participants in Study AG10-202 received 800 mg acoramidis HCl BID.

Study AG10-301 (ATTRibute-CM Trial) was a randomised, double-blind, placebo-controlled clinical trial conducted globally to assess the safety and efficacy of acoramidis in patients with ATTR-CM (both variant and wild-type). All participants who completed 30 months of blinded treatment in Study AG10-301 and the final assessments of the double-blind treatment period (month 30 visit) were invited to participate in an OLE study of long-term acoramidis treatment (Study AG10-304).

Most of the safety data for acoramidis were contributed by Study AG10-301, comparing acoramidis with placebo in patients with ATTR-CM.

In addition, data from Study AG10-301 and the two ongoing OLE studies (AG10-202 and AG10-304) have been analysed in two integrated safety data pools:

Pool 1 - Open-label Extension Studies:

Data pool for safety assessments collected during uncontrolled open-label treatment periods.
The objective of this pool was to evaluate the long-term safety profile of acoramidis by summarizing the safety data collected in the two OLE studies, AG10-202 and AG10-304. The safety data collected in the parent studies for each participant were not included in the integrated safety data of this pool.

Pool 2 - Integrated Acoramidis Treatment Exposure and AE Data:

Data pool for acoramidis treatment exposure in patients (across the randomised and placebo-controlled and uncontrolled open-label treatment periods) and AE safety data while on acoramidis treatment.
The objective of this pool was to provide an accurate accounting of cumulative acoramidis treatment exposure for each participant in Studies AG10-202, AG10-301 and AG10-304, taking into consideration

Study AG10-304 participants' treatment allocation in Study AG10-301. This integrated data pool also aimed to provide a summary of exposure-adjusted incidence rate and event rate of acoramidis TEAEs. Treatment exposure and AE data from Studies AG10-202, AG10-301, and AG10-304 were included in the integrated safety data of this pool. For the participants in Study AG10-304 who were treated with placebo in Study AG10-301, AEs reported during the double-blind treatment period in Study AG10-301 and AEs reported during the open-label treatment period in Study AG10-304 are summarised separately.

The data cut-off dates for the ongoing OLE studies are 06 January 2023 for Study AG10-202 and 27 February 2023 for Study AG10-304.

Safety data from the respective CSRs were presented by individual study for Phase 2 Study AG10-201 in patients with ATTR-CM and the Phase 1 studies in healthy adult volunteers (Studies AG10-001, AG10-003, AG10-004, AG10-005, AG10-007, AG10-008, and ALXN2060-HV-101). Data for deaths, SAEs, and TEAEs leading to study withdrawal as of the visit cut-off date of 10 January 2023 are also summarised for Phase 3 Study ALXN2060-TAC-302 conducted in Japan in patients with ATTR-CM.

Table 19: Summary of Studies Included in the Summary of Clinical Safety

Study	Study Design	Study Population	Dose Regimen Evaluated[a]	Number of Healthy Adult Volunteers or Patients with ATTR-CM			Study Status (as of 06 July 2023)
				Acoramidis	Placebo	Total	
Phase 3 Studies							
AG10-301	Randomised, double-blind, placebo-controlled study of the efficacy and safety of acoramidis	Patients with symptomatic ATTR-CM	800 mg acoramidis HCl or placebo BID	421	211	632	Completed
AG10-304	Open-label extension and safety evaluation study of acoramidis	Patients with symptomatic ATTR-CM who completed Study AG10-301	800 mg acoramidis HCl BID	312	0	312[b]	Ongoing[c]
ALXN2060-TAC-302[d]	Open label, 2-part study of efficacy, safety, PK, and PD of acoramidis	Japanese patients with symptomatic ATTR-CM	800 mg acoramidis HCl BID	25	0	25	Ongoing
Phase 2 Studies							
AG10-201	Randomised, placebo-controlled, dose-ranging study of the safety, tolerability, PK, and PD of acoramidis	Patients with symptomatic ATTR-CM	400 mg or 800 mg acoramidis HCl or placebo BID for 28 days	32	17	49	Completed

Study	Study Design	Study Population	Dose Regimen Evaluated[a]	Number of Healthy Adult Volunteers or Patients with ATTR-CM			Study Status (as of 06 July 2023)
				Acoramidis	Placebo	Total	
AG10-202	Open-label extension and safety evaluation study	Patients with symptomatic ATTR-CM who completed Study AG10-201	800 mg acoramidis HCl BID	47[e]	0	47	Ongoing[f]
Phase 1 Studies							
AG10-001	Randomised, placebo-controlled, single and multiple ascending dose study of the safety, tolerability, PK, and PD of acoramidis	Healthy adult volunteers	Single dose: 50, 150, 300, 800 mg acoramidis HCl or placebo	24	8	32	Completed
			Multiple doses: 100, 300, 800 mg acoramidis HCl q12h or placebo for 12 days	18	6	24	
AG10-003	Open-label, single-dose, 2-way crossover bioequivalence study of two acoramidis tablet formulations	Healthy adult volunteers	Single dose of acoramidis administered as two tablets of 200 mg acoramidis HCl or one tablet of 400 mg acoramidis HCl	24	0	24	Completed
AG10-004	Randomised, open-label, 2-way crossover, single-dose study of the safety, tolerability, PK of acoramidis	Healthy Japanese and non-Japanese adult volunteers	Single dose of 400 mg or 800 mg acoramidis HCl in Period 1 followed by a 7-day washout period and crossover to the other dose in Period 2	19	0	19	Completed

Study	Study Design	Study Population	Dose Regimen Evaluated[a]	Number of Healthy Adult Volunteers or Patients with ATTR-CM			Study Status (as of 06 July 2023)
				Acoramidis	Placebo	Total	
AG10-005	Randomised, placebo-controlled, single ascending dose study of the safety, tolerability, PK and PD of supratherapeutic doses of acoramidis	Healthy adult volunteers	Single dose of 1200, 1600, and 2000 mg of acoramidis HCl or placebo	18	9	27	Completed
AG10-007	Open-label ADME study of oral [^{14}C]-acoramidis	Healthy adult volunteers	Single dose of 800 mg (~450 µCi) [^{14}C]-acoramidis HCl (oral suspension)	6	0	6	Completed
AG10-008	Open-label, 2-part, 2-period study to assess the effect of acoramidis on the PK of OAT1/OAT3 substrates adefovir and oseltamivir carboxylate	Healthy adult volunteers	Part 1: Single dose of 10 mg adefovir dipivoxil and 800 mg acoramidis HCl q12h for 8 days plus a single dose of 10 mg adefovir dipivoxil on the 7th day Part 2: Single dose of 75 mg oseltamivir phosphate and 800 mg acoramidis HCl q12h for 9 days plus a single dose of 75 mg oseltamivir phosphate on the 7th day	32 (14 Part 1; 18 Part 2)	0	32	Completed
ALXN2060-HV-101[d]	Randomised, open-label, 2-period, 2-sequence, 2-way crossover food effect study of acoramidis	Healthy adult volunteers	Single dose of 800 mg acoramidis HCl fasted or fed	18	0	18	Completed

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; ATTR-CM = transthyretin amyloid cardiomyopathy; BID = twice daily; HCl = hydrochloride; OAT = organic anion transporter; OLE = open-label extension; PD = pharmacodynamic(s); q12h = every 12 hours; PK = pharmacokinetic(s)

[a] A historical naming convention defined doses on the acoramidis HCl salt basis; the 44.5, 89, 133.5, 267, 356, 712, 1068, 1424, and 1780 mg acoramidis doses are synonymous with 50, 100, 150, 300, 400, 800, 1200, 1600, and 2000 mg “AG10” or “acoramidis HCl” doses, respectively.
[b] Included participants who completed Study AG10-301. As of the data cut-off date of 27 February 2023, 312 participants were enrolled in Study AG10-304 and 300 participants had received open-label treatment with 800 mg acoramidis HCl BID. The summary tables herein present data for these 300 participants.
[c] Safety data for ongoing OLE Study AG10-304 up to the visit cut-off date of 27 February 2023 are included in the integrated analyses.
[d] Sponsored by Eidos partner, Alexion Pharmaceuticals, GK.
[e] Included participants who completed Study AG10-201.
[f] Safety data for ongoing OLE Study AG10-202 up to the visit cut-off date of 06 January 2023 are included in the integrated analyses. An interim CSR with a data cut of 31 August 2021 is submitted in the application.

2.6.8.1. Patient exposure

Table 20: Extent of Exposure to Acoramidis in the Clinical Programme

Study	Phase	Number of Participants Treated with Acoramidis			Number of Participants Treated with Placebo
		Any Exposure	≥ 6 months	≥ 1 Year	
AG10-001 SAD	1	24			8
AG10-001 MAD	1	18			6
AG10-003	1	24			0
AG10-004	1	19			0
AG10-005	1	18			9
AG10-006[a]	1	14			0
AG10-007	1	6			0
AG10-008	1	32			0
AG10-009[b]	1	28			0
ALXN2060-HV-101	1	18			0
AG10-201	2	32[c]			17
AG10-202 OLE to AG10-201	2	47	41	37	NA
AG10-301	3	421	385	365	211
AG10-304 OLE to AG10-301	3	95[d]	43	6	NA
ALXN2060-TAC-302	3	25	23	22	0
AG10-999[e]	1	1			

Abbreviations: MAD = multiple ascending dose; NA = not applicable; OLE = open-label extension; SAD = single ascending dose
[a] Study AG10-006 is not included in the application.
[b] Study AG10-009 is not included in the application.

[c] A total of 30 participants from the acoramidis treatment arm in Study AG10-201 transitioned to ongoing Study AG10-202 and are included in the "Any Exposure" column of Study AG10-202.
[d] Placebo participants from Study AG10-301; in total, 312 participants from Study AG10-301 had transitioned to ongoing Study AG10-304 and 300 have received OLE treatment as of 27 February 2023.
[e] Expanded access study.

Table 21: Summary of Extent of Acoramidis Treatment Exposure – Integrated Acoramidis Treatment Safety Analysis Set

	AG10-202 Participants and AG10-301 Participants Treated with Acoramidis[a] (N = 468)	AG10-304 Participants Previously Treated with Placebo in AG10-301 (N = 95)	Overall (N = 563)
Duration of treatment exposure (years)[b]			
N	468	95	563
Mean (SD)	2.376 (1.0467)	0.456 (0.3276)	2.052 (1.2027)
Median (Q1, Q3)	2.491 (1.814, 3.044)	0.476 (0.167, 0.695)	2.467 (0.860, 2.951)
Min, Max	0.01, 4.42	0.00, 1.32	0.00, 4.42
Duration of treatment exposure			
≥ 1 year	402 (85.9%)	6 (6.3%)	408 (72.5%)
≥ 2 years	343 (73.3%)	0 (0.0%)	343 (60.9%)
≥ 2.5 years	231 (49.4%)	0 (0.0%)	231 (41.0%)
≥ 3 years	127 (27.1%)	0 (0.0%)	127 (22.6%)
≥ 4 years	25 (5.3%)	0 (0.0%)	25 (4.4%)
≥ 5 years	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: Max = maximum; Min = minimum; N = total number of participants; Q = quartile; SD = standard deviation
[a] Study AG10-301 participants treated with acoramidis include those who did not enter Study AG10-304 and Study AG10-304 participants previously treated with acoramidis in Study AG10-301.
[b] Duration of treatment exposure (years) is calculated as: Duration of treatment exposure = (Last dosing date of acoramidis treatment – First dosing date of acoramidis treatment + 1) / 365.25.

Data from the current OLE study AG10-304, as from data cut-off 27 February 2023, included only 0.496 years median duration of open-label treatment with 800 mg acoramidis HCl BID.

ATTR amyloidosis is a chronic progressive disease, and the treatment with acoramidis is expected to be long-term. Further close safety vigilance is expected for this long-term study.

The applicant provided a review of new safety data for OLE Study AG10-304 and Study AG10-202. No new relevant safety issues were identified, and so the safety profile is considered unchanged.

2.6.8.2. Adverse events

Overall Summary of Adverse Events

Phase 3 Study AG10-301

Most participants in either treatment group (> 97%) experienced at least one TEAE.

Table 22: Overall Summary of Treatment-emergent Adverse Events in Study AG10-301 – Safety Population

Participants with One or More Event(s)	Acoramidis (N = 421) n (%) E[a]	Placebo (N = 211) n (%) E[a]
Any TEAE	413 (98.1%) 4234	206 (97.6%) 2314
TEAE with fatal outcome	60 (14.3%) 66	36 (17.1%) 38
TEAE leading to hospitalisation	212 (50.4%) 542	128 (60.7%) 350
TEAE leading to study drug discontinuation	39 (9.3%) 46	18 (8.5%) 22
TEAE leading to dose reduction[b]	4 (1.0%) 4	0
Any treatment-emergent SAE	230 (54.6%) 592	137 (64.9%) 376
Treatment-emergent SAE leading to study drug discontinuation	21 (5.0%) 25	15 (7.1%) 16
Treatment-emergent SAE leading to dose reduction	2 (0.5%) 2	0
Any treatment-related TEAE[c]	50 (11.9%) 76	11 (5.2%) 15
Treatment-related treatment-emergent SAE	2 (0.5%) 3	0
Severe TEAE[d]	157 (37.3%) 367	96 (45.5%) 217

Abbreviations: n = number of participants experiencing a TEAE (the participant is counted only once for each event), N = total number of participants in the study arm; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] % is of the column total. E is the number of events.
[b] Dose reduction was not allowed for participants enrolled after Protocol Amendment 3.
[c] Relationship to study drug as assessed by the Investigator.
[d] Severity as assessed by the Investigator.

Common Adverse Events

Phase 3 Study AG10-301

The incidence of TEAEs reported in > 10% of participants (for any PT in either treatment group) is summarised by treatment group for the Safety Population in the next table.

Table 23: Treatment-emergent Adverse Events Occurring in > 10% of Participants in Either Treatment Group in Study AG10-301 – Safety Population

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
Any Treatment-emergent Adverse Event	413 (98.1%) 4234	206 (97.6%) 2314
Cardiac Disorders	230 (54.6%) 498	144 (68.2%) 397
Cardiac failure	101 (24.0%) 167	83 (39.3%) 166
Atrial fibrillation	70 (16.6%) 77	46 (21.8%) 59
Infections and Infestations	246 (58.4%) 501	116 (55.0%) 240
COVID-19	89 (21.1%) 89	30 (14.2%) 32
Urinary tract infection	51 (12.1%) 62	28 (13.3%) 34
Gastrointestinal Disorders	221 (52.5%) 445	98 (46.4%) 185
Constipation	52 (12.4%) 58	32 (15.2%) 38
Diarrhoea	49 (11.6%) 56	16 (7.6%) 17
Musculoskeletal and Connective Tissue Disorders	184 (43.7%) 336	83 (39.3%) 165

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
Arthralgia	48 (11.4%) 62	23 (10.9%) 32
Nervous System Disorders	182 (43.2%) 283	77 (36.5%) 128
Dizziness	46 (10.9%) 55	23 (10.9%) 24
Metabolism and Nutrition Disorders	149 (35.4%) 262	85 (40.3%) 158
Gout	47 (11.2%) 67	17 (8.1%) 23
Respiratory, Thoracic and Mediastinal Disorders	146 (34.7%) 263	86 (40.8%) 142
Dyspnoea	52 (12.4%) 62	40 (19.0%) 56
General Disorders and Administration Site Conditions	144 (34.2%) 219	79 (37.4%) 130
Fatigue	42 (10.0%) 48	26 (12.3%) 28
Oedema peripheral	33 (7.8%) 36	25 (11.8%) 28
Injury, Poisoning and Procedural Complications	137 (32.5%) 292	81 (38.4%) 180
Fall	67 (15.9%) 96	39 (18.5%) 62
Renal and Urinary Disorders	142 (33.7%) 216	64 (30.3%) 99
Acute kidney injury	52 (12.4%) 64	22 (10.4%) 30

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

In the gastrointestinal disorders SOC, the 6.1% higher incidence of TEAEs in the acoramidis treatment group compared to placebo was primarily driven by the events of diarrhoea (acoramidis: 11.6%; placebo: 7.6%); abdominal pain upper (acoramidis: 5.5%; placebo: 1.4%); and abdominal pain (acoramidis: 4.3%; placebo: 2.4%).

In the nervous system disorders SOC, the 6.7% higher incidence of TEAEs in the acoramidis treatment group compared to placebo was primarily driven by the events of paraesthesia, presyncope, neuropathy peripheral, cognitive disorder, hypoesthesia, dizziness postural, balance disorder, sciatica, somnolence, memory impairment, dysgeusia, aphasia, cerebral infarction, burning sensation, nervous system disorder, ischaemic stroke, polyneuropathy, subarachnoid haemorrhage, and trigeminal neuralgia (incidence range: 0.5%-1.7% higher in the acoramidis treatment group compared to placebo). These terms were varied and there were no discernible patterns of clinical meaning.

TEAEs in the SOC of gastrointestinal disorders (specially diarrhoea, nausea, abdominal discomfort and abdominal pain) and rash, consistently appears as a common TEAEs in the different studies and analysis. Although these symptoms and signals are often associated with the disease, there appears to be a statistically significant difference between the treatment group and placebo. The applicant was requested to analysis furthermore this topic and it is encouraged to have gastrointestinal disorders, rash and blood creatinine increased as possible adverse reactions in the tabulated list of adverse reactions. Moreover, the applicant was invited to discuss whether GI AEs were more frequent in the ATTRv than on the ATTRwt population. Diarrhoea is of particular concern in ATTRv population. The applicant updated section 4.8 Undesirable effects in the SmPC with information about diarrhoea, as requested.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Phase 3 Study AG10-301

The incidence of TEAEs leading to a fatal outcome was proportionately lower in the acoramidis treatment group than in the placebo group (14.3% versus 17.1%). The SAEs leading to death were consistent with progression of cardiomyopathy and other comorbidities expected for this population. None of the TEAEs leading to fatal outcome were considered related to study drug by the Investigator.

The most common TEAEs leading to fatal outcome in both groups were in the SOC of cardiac disorders, specifically the PT of cardiac failure (acoramidis, 4.3%; placebo, 3.8%). For all other TEAEs leading to fatal outcome, a difference of 2.3% between-groups (8.6% in the acoramidis group, 10.9% in the placebo group) was reported for the cardiac disorders. All other SOCs with TEAEs leading to fatal outcome had a difference of < 1% between the treatment groups. The cumulative incidence curve of time to TEAEs leading to fatal outcome demonstrated that both treatment groups were similar through month 12, with the frequency higher in the acoramidis group in months 15 and 18, and the frequency higher in the placebo group in months 24 to 30. The divergent incidences of TEAEs leading to fatal outcome in months 24 to 30 were primarily driven by the difference in cardiac disorders, with three participants in each treatment group (acoramidis, 0.7%; placebo, 1.4%) experiencing fatal TEAEs with an onset of day 720 or later.

A summary of TEAEs that led to death is provided in the next table.

Table 24: Treatment-emergent Adverse Events Leading to Fatal Outcome (Reported in More than One Participant for any PT in Either Treatment Group) in Study AG10-301 – Safety Population

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
Any TEAE Leading to Fatal Outcome	60 (14.3%) 66	36 (17.1%) 38
Cardiac Disorders	36 (8.6%) 36	23 (10.9%) 23
Cardiac failure	18 (4.3%) 18	8 (3.8%) 8
Cardiac failure chronic	5 (1.2%) 5	2 (0.9%) 2
Cardiac arrest	2 (0.5%) 2	3 (1.4%) 3
Cardiac amyloidosis	2 (0.5%) 2	2 (0.9%) 2
Cardiac failure congestive	2 (0.5%) 2	1 (0.5%) 1
Cardiorenal syndrome	0	3 (1.4%) 3
Right ventricular failure	1 (0.2%) 1	2 (0.9%) 2
Cardiac failure acute	2 (0.5%) 2	0
Infections and Infestations	8 (1.9%) 8	3 (1.4%) 3
Septic shock	3 (0.7%) 3	0
COVID-19	2 (0.5%) 2	0

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
COVID-19 pneumonia	0	2 (0.9%) 2
Staphylococcal bacteraemia	2 (0.5%) 2	0
General Disorders and Administration Site Conditions	5 (1.2%) 5	3 (1.4%) 3
Death	3 (0.7%) 3	1 (0.5%) 1

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

Integrated Acoramidis Treatment - Studies AG10-202, AG10-301 and AG10-304

The most common TEAEs with a fatal outcome were in the SOC of cardiac disorders, specifically the PTs of cardiac failure (EAIR 2.1) and cardiac failure chronic (EAIR 0.5). The SAEs leading to death were consistent with progression of cardiomyopathy and other comorbidities expected for this population. None of the TEAEs leading to fatal outcome were considered related to study drug by the Investigator.

Other Serious Adverse Events

Phase 3 Study AG10-301

The overall incidence of SAEs was lower in the acoramidis treatment group than in the placebo group (54.6% versus 64.9%). Most SAEs were attributable to the underlying disease. The most frequently reported SAEs (by SOC, > 20% of participants in both treatment groups) were in the SOC of cardiac disorders (acoramidis: 27.8%; placebo: 39.3%). The most frequently reported SAEs (by PT, > 3% in either treatment group) were cardiac failure (acoramidis: 10.7%; placebo: 18.5%); cardiac failure acute (acoramidis: 5.0%; placebo: 6.6%); atrial fibrillation (acoramidis: 4.5%; placebo: 7.1%); acute kidney injury (acoramidis: 5.0%; placebo: 3.8%); fall (acoramidis: 3.1%; placebo: 0.9%); and COVID-19 pneumonia (acoramidis: 0.5%; placebo: 3.8%).

The incidence of SAEs reported in > 1% of participants (for any PT in either treatment group) is summarised by treatment group for the Safety Population in the next table.

Table 25: Serious Treatment-emergent Adverse Events Reported in > 1% of Participants in Either Treatment Group in Study AG10-301 – Safety Population

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
Participant with Any Treatment-emergent SAE	230 (54.6%) 592	137 (64.9%) 376
Cardiac Disorders	117 (27.8%) 193	83 (39.3%) 177
Cardiac failure	45 (10.7%) 64	39 (18.5%) 77
Cardiac failure acute	21 (5.0%) 28	14 (6.6%) 19
Atrial fibrillation	19 (4.5%) 19	15 (7.1%) 18
Bradycardia	11 (2.6%) 11	2 (0.9%) 2
Ventricular tachycardia	6 (1.4%) 6	5 (2.4%) 11

System Organ Class Preferred Term	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
Atrioventricular block complete	8 (1.9%) 8	3 (1.4%) 3
Acute myocardial infarction	5 (1.2%) 7	4 (1.9%) 4
Cardiac failure chronic	6 (1.4%) 6	3 (1.4%) 4
Cardiac arrest	4 (1.0%) 4	4 (1.9%) 4
Cardiac failure congestive	5 (1.2%) 5	3 (1.4%) 3
Cardiorenal syndrome	3 (0.7%) 3	3 (1.4%) 4
Atrial flutter	3 (0.7%) 3	3 (1.4%) 3
Cardiogenic shock	1 (0.2%) 1	3 (1.4%) 5
Infections and Infestations	62 (14.7%) 91	37 (17.5%) 44
Pneumonia	12 (2.9%) 13	6 (2.8%) 6
COVID-19	9 (2.1%) 9	4 (1.9%) 4
Urinary tract infection	7 (1.7%) 8	3 (1.4%) 3
COVID-19 pneumonia	2 (0.5%) 2	8 (3.8%) 8
Cellulitis	7 (1.7%) 7	3 (1.4%) 3
Injury, Poisoning and Procedural Complications	41 (9.7%) 55	16 (7.6%) 18
Fall	13 (3.1%) 13	2 (0.9%) 2
Rib fracture	5 (1.2%) 5	0
Gastrointestinal Disorders	34 (8.1%) 41	16 (7.6%) 18
Inguinal hernia	6 (1.4%) 6	2 (0.9%) 2
Nervous System Disorders	32 (7.6%) 35	13 (6.2%) 17
Syncope	6 (1.4%) 6	4 (1.9%) 5
Presyncope	5 (1.2%) 5	1 (0.5%) 1
Renal and Urinary Disorders	30 (7.1%) 37	11 (5.2%) 11
Acute kidney injury	21 (5.0%) 21	8 (3.8%) 8
Respiratory, Thoracic and Mediastinal Disorders	18 (4.3%) 25	9 (4.3%) 10
Pleural effusion	2 (0.5%) 2	4 (1.9%) 4
Dyspnoea	2 (0.5%) 2	3 (1.4%) 3
Musculoskeletal and Connective Tissue Disorders	14 (3.3%) 15	12 (5.7%) 12
Osteoarthritis	3 (0.7%) 3	4 (1.9%) 4
Musculoskeletal chest pain	1 (0.2%) 1	3 (1.4%) 3
Vascular Disorders	14 (3.3%) 14	8 (3.8%) 8
Orthostatic hypotension	3 (0.7%) 3	4 (1.9%) 4
Metabolism and Nutrition Disorders	11 (2.6%) 13	8 (3.8%) 10
Hypervolaemia	3 (0.7%) 4	5 (2.4%) 7
Blood and Lymphatic System Disorders	9 (2.1%) 12	3 (1.4%) 7
Anaemia	7 (1.7%) 9	2 (0.9%) 4

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; E = event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants experiencing a treatment-emergent serious adverse event (the participant

is counted only once for each serious AE); N = total number of participants in the study arm; SAE = serious adverse event; TEAE = treatment-emergent adverse event
% is of the column total. E is the number of events for system organ class or preferred term.
An SAE that occurred more than 30 days after the last dose of study drug was not counted as a TEAE. System organ class and preferred term coded using MedDRA Version 24.1.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product

Treatment-related Serious Adverse Events (Study AG10-301)

There were no related SAEs, as assessed by the Investigator, reported in the placebo group. In the acoramidis treatment group, three related SAEs, as assessed by the Investigator, were reported in two participants (0.5%; PTs of cardiac failure acute in a single participant, and syncope and hypotension in another participant). These SAEs are described below. The Sponsor assessed these SAEs as not related to study drug.

Serious, Unexpected, Related (as Assessed by Investigator)

Cardiac failure acute

The Investigator assessed the event of cardiac failure acute as related to stopping the study drug 12 days prior to the event.

The Sponsor assessed the event of cardiac failure acute as not related to acoramidis treatment. ATTR-CM is a progressive, fatal disease characterised by progressive left and right heart failure. The participant's underlying condition of ATTR-CM including unstable angina, coronary artery disease, hypertension, atrial fibrillation, chronic systolic and diastolic heart failure, and ischemic cardiomyopathy provided likely aetiologies for the event in this case.

Hypotension

The Investigator considered furosemide, perindopril, and sotalol as co-suspect drugs. The Investigator's rationale for reporting causality was that the new drug may or may not have hypotension as a side effect and cannot rule out that possibility, hence in a binary reporting system 'possibly' or 'definitely' causal relationships are equivalent.

The Sponsor assessed the event hypotension as not related to acoramidis.

Syncope

The Investigator reported perindopril, sotalol, and furosemide were co-suspect drugs and reported not being able to exclude a relationship between the syncope and study drug. Therefore, he was unable to provide an "unrelated" causation.

The Sponsor assessed the event of syncope as not related to acoramidis.

2.6.8.4. Laboratory findings

Haematology

No significant values were identified.

Clinical Chemistry

There was no clinically meaningful difference in incidence of thyroid adverse events, with hypothyroidism reported for 3.6% of participants in the acoramidis treatment group and for 2.8% in the placebo group. There was one SAE of hypothyroidism in the acoramidis group reported by the

Investigator as not related to study drug, instead related to the participant's history of subclinical hypothyroidism and amiodarone administration, with elevated thyroid peroxidase antibodies and development of Hashimoto's thyroiditis. The Sponsor agreed the hypothyroidism was not related to acoramidis. No clinically meaningful impact on thyroid function was observed in either treatment group. Review of reported TEAEs (non-serious and serious) did not identify a clinically meaningful imbalance in thyroid events.

Urinalysis

No significant values were identified.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Age and Sex

Patients diagnosed with ATTR-CM tend to be male, and on average are aged 60 years or older. Most of the participants were male in Phase 3 study AG10-301 (90%) and Phase 2 study AG10-201 (92%). The majority of participants were elderly (≥ 65 years of age) in Phase 3 study AG10-301 (median age 78.0 years) and Phase 2 study AG10-201 (median age, 73.0 years).

Race

The majority of the participants were White in Phase 3 study AG10-301 (88%) and Phase 2 study AG10-201 (71%), precluding the meaningful analyses of AEs by race subgroups in these studies.

In Phase 1 Study AG10-004, single doses of 400 mg and 800 mg acoramidis HCl were generally well tolerated without safety signals of potential concern in healthy Japanese (n = 9) and non-Japanese (n = 10) adults. No clinically meaningful differences were noted between the safety profiles of the study participants. In total, six TEAEs were reported in four of the 19 participants (PTs tinnitus, visual field defect in one non-Japanese participant; PTs respiratory tract infection, nausea in one non-Japanese participant; PT light-headedness in one Japanese participant; PT muscle strain in one non-Japanese participant).

Renal Impairment

For the subgroup of participants with eGFR < 30 mL/1.73 m^2 at Screening, severe TEAEs were reported in 8/12 (66.7%) participants in the acoramidis group and 3/9 (33.3%) participants in the placebo group. In this subgroup of participants with eGFR < 30 mL/min/1.73 m^2, severe TEAEs of cardiac failure (PT) were reported in two participants (16.7%) in the acoramidis group; the remaining severe TEAEs were reported in one participant each. Severe TEAEs with fatal outcome were reported for the PTs of cardiac failure, cerebral infarction, septic shock, and Staphylococcal bacteraemia (one participant [8.3%] each) in the acoramidis group, and for the PT of gastrointestinal cancer metastatic for one participant (11.1%) in the placebo group.

There were no remarkable differences in all safety and laboratory assessments in the eGFR groups. The number of participants in the eGFR < 30 mL/min/1.73 m^2 group was too small to draw definitive conclusions (N = 12 in the acoramidis treatment group; N = 9 in the placebo group). No safety signals

of potential clinical concern were identified for acoramidis in participants in the eGFR < 30 mL/min/1.73 m^2 subgroup.

An overview of TEAEs is summarised by eGFR group for the Safety Population in the next table.

Table *26*: Overall Summary of TEAEs in Study AG10-301 by eGFR Subgroup – Safety Population

Participants with One or More Event(s)	eGFR ≥ 30 mL/min/1.73 m^2		eGFR < 30 mL/min/1.73 m^2	
	Acoramidis (N = 409) n (%) E	Placebo (N = 202) n (%) E	Acoramidis (N = 12) n (%) E	Placebo (N = 9) n (%) E
Any TEAE	402 (98.3%) 4145	197 (97.5%) 2202	11 (91.7%) 89	9 (100.0%) 112
TEAE with fatal outcome	56 (13.7%) 62	35 (17.3%) 37	4 (33.3%) 4	1 (11.1%) 1
TEAE leading to hospitalisation	204 (49.9%) 520	120 (59.4%) 337	8 (66.7%) 22	8 (88.9%) 13
TEAEs leading to study drug discontinuation	36 (8.8%) 42	16 (7.9%) 19	3 (25.0%) 4	2 (22.2%) 3
TEAEs leading to dose reduction	4 (1.0%) 4	0	0	0
Any treatment-emergent SAE	221 (54.0%) 568	129 (63.9%) 363	9 (75.0%) 24	8 (88.9%) 13
Treatment-emergent SAEs leading to study drug discontinuation	20 (4.9%) 24	14 (6.9%) 14	1 (8.3%) 1	1 (11.1%) 2
Treatment-emergent SAEs leading to dose reduction	2 (0.5%) 2	0	0	0
Any treatment-related TEAE	45 (11.0%) 67	10 (5.0%) 11	5 (41.7%) 9	1 (11.1%) 4
Treatment-related treatment-emergent SAEs	2 (0.5%) 3	0	0	0
Severe TEAE	149 (36.4%) 346	93 (46.0%) 209	8 (66.7%) 21	3 (33.3%) 8

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate; n = number of participants experiencing a TEAE (the participant was counted only once for each AE); N = total number of participants in the study arm; SAE = serious adverse event; TEAE = treatment-emergent adverse event
% is of the column total. E is the number of events.
Relationship to study drug as assessed by the Investigator.
An AE that occurred more than 30 days after the last dose of study drug was not counted as a TEAE.

Hepatic Impairment

Acoramidis has not been studied in patients with hepatic impairment.

The clinical studies with acoramidis in patients with symptomatic ATTR-CM restricted study entry to patients with normal hepatic function and mild hepatic impairment. The studies required ALT and AST ≤ 3 × ULN and total bilirubin ≤ 3 × ULN (≤ 2 × ULN in Phase 2 Study AG10-201) at Screening.

Use in Pregnancy and Lactation

There are no data on the use of acoramidis in pregnant women. There are no available data on the presence of acoramidis in either human or animal milk or the effects of the drug on breastfed infants or maternal milk production. Pregnant and lactating women were excluded from studies of acoramidis,

and female participants of childbearing potential were obliged to use a highly effective method of contraception beginning with randomisation and continuing for 30 days after the last dose of acoramidis described in the clinical study protocols.

In Study AG10-001, there was one healthy adult participant who became pregnant while in the study. Repeated attempts to contact the participant for follow-up regarding pregnancy outcomes were unsuccessful.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Drug/Food Interaction

There were no trends noted between fed/fasted states in AEs experienced by healthy participants during Part A (SAD) in the FIH, Phase 1 Study AG10-001 or in crossover Study ALXN2060-HV-101.

Drug/Drug Interaction

Multiple oral doses of acoramidis, coadministered with a single dose of adefovir or oseltamivir, were generally well tolerated by the healthy adult participants in the study.

2.6.8.8. Discontinuation due to adverse events

Please see discussion in common AEs.

2.6.8.9. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The evaluation of the safety of acoramidis is based on 12 clinical studies, including seven Phase 1 studies in healthy adult volunteers (Studies AG10-001, AG10-003, AG10-004, AG10-005, AG10-007, AG10-008 and ALXN2060-HV-101), two Phase 2 studies in patients with symptomatic ATTR-CM (double-blind Study AG10-201 and the ongoing OLE study to Study AG10-201 [Study AG10-202]), and three Phase 3 studies in patients with symptomatic ATTR-CM (pivotal Study AG10-301, ongoing OLE study to Study AG10-301 [Study AG10-304], and Study ALXN2060-TAC-302 conducted in Japan). In addition, an SAE narrative was provided for the single patient with ATTR-CM enrolled in the Phase 1 Expanded Access use study (Study AG10-999). Most of the safety data available for acoramidis were contributed by Study AG10-301, comparing acoramidis with placebo in patients with ATTR-CM. In addition, data from Study AG10-301 and the two ongoing OLE studies (AG10-202 and AG10-304) have been analysed in two integrated safety data pools, one for the open-label extension studies (to evaluate long-term safety profile of acoramidis) and other for integrated acoramidis treatment exposure and AE data (to provide cumulative safety data).

In total, there have been 792 participants exposed to acoramidis throughout the clinical programme. The median duration of exposure to 800 mg acoramidis HCl BID was 2.47 years (N = 563), with 343 (60.9%) participants receiving acoramidis for ≥ 2 years, and 25 (4.4%) receiving ≥ 4 years treatment.

As of data cut-of 27 February 2023, 300 of the 312 participants enrolled in Study AG10-304 (including 205 participants who were in the acoramidis arm in Study AG10-301) had received open-label treatment with 800 mg acoramidis HCl BID for a median duration of 0.496 years. Being ATTR amyloidosis a chronic progressive disease, the treatment with acoramidis is expected to be long-term. Further close safety vigilance is expected for this long-term study.

Study AG10-301

In the pivotal 30-month Phase 3 study (ATTRibute-CM), acoramidis was safe and generally well tolerated. Overall, the pattern of TEAEs was consistent with the disease under study and co-morbidities expected for the ATTR-CM population (mean age of the patients was 77.3 ±6.6 years).

Similar proportions of participants in the acoramidis and placebo groups discontinued study drug because of a TEAE (acoramidis: 9.3%; placebo: 8.5%).

The overall incidence of adverse events during treatment was similar in the acoramidis group and the placebo group (98.1% and 97.6%, respectively) and favoured acoramidis compared to placebo with respect to serious adverse events (54.6% vs. 64.9%), TEAEs leading to hospitalisation (50.4% vs. 60.7%) and TEAEs with a fatal outcome (14.3% vs. 17.1%).

The overall incidences of serious TEAEs (acoramidis, 54.6%; placebo, 64.9%), TEAEs with fatal outcome (acoramidis, 14.3%; placebo, 17.1%), severe TEAEs (acoramidis, 37.3%; placebo, 45.5%), and TEAEs leading to hospitalisation (acoramidis, 50.4%; placebo, 60.7%) were lower in the acoramidis treatment group than in the placebo group. The incidence of discontinuations due to TEAEs was low and similar in both groups (acoramidis: 9.3%; placebo: 8.5%).

The majority of TEAEs were mild or moderate in severity (acoramidis: 60.8%; placebo: 52.1%). Severe TEAEs were reported for 37.3% of participants in the acoramidis group vs. 45.5% in the placebo group.

Most common TEAEs were cardiac failure (acoramidis: 24.0%; placebo: 39.3%), atrial fibrillation (acoramidis: 16.6%; placebo: 21.8%), COVID-19 (acoramidis: 21.1%; placebo: 14.2%), dyspnoea (acoramidis: 12.4%; placebo: 19.0%), constipation (acoramidis: 12.4%; placebo: 15.2%), diarrhoea (acoramidis: 11.6%; placebo: 7.6%), gout (acoramidis: 11.2%; placebo: 8.1%) and fall (acoramidis: 15.9%; placebo: 18.5%).

Most frequently reported SAEs (by PT, >3% in either treatment group) included cardiac failure (acoramidis: 10.7%; placebo: 18.5%), cardiac failure acute (acoramidis: 5.0%; placebo: 6.6%), atrial fibrillation (acoramidis: 4.5%; placebo: 7.1%), acute kidney injury (acoramidis: 5.0%; placebo: 3.8%), COVID-19 pneumonia (acoramidis: 0.5%; placebo: 3.8%) and fall (acoramidis: 3.1%; placebo: 0.9%). Fall safety data were consistent with the aging patient population under study and no clinically meaningful imbalance in TEAEs or SAEs was observed between the treatment groups. There was no evidence to establish a causal relationship between acoramidis and fall.

The incidence of TEAEs leading to a fatal outcome was proportionately lower in the acoramidis treatment group than in the placebo group (14.3% versus 17.1%). The most common TEAEs leading to fatal outcome in both groups were in the SOC of cardiac disorders, specifically the PT of cardiac failure (acoramidis, 4.3%; placebo, 3.8%).

Findings from vital signs, ECG and physical examination were consistent with the patient population under study. Mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate were similar in both treatment groups. The mean ECG intervals at baseline in both treatment groups were consistent and did not markedly change throughout the duration of the study.

There was no clinically meaningful difference in laboratory parameters (haematology and clinical chemistry) between treatment groups except for a slight non-progressive increase in creatinine (approximately 15%) and decrease in eGFR (acoramidis: -8.2 mL/min and Placebo: -0.7 mL/min) which were most pronounced at day 28. The applicant explained the increase in serum creatinine and decrease in eGFR with an effect of acoramidis on renal haemodynamics. The applicant was asked to clarify, by which mechanism of action acoramidis could exert renal hemodynamic effects with lowering intraglomerular pressure. In addition, the applicant was asked to justify the higher percentage of acute kidney injury (AE: acoramidis: 12.4% vs. placebo: 10.4%; SAE: acoramidis: 5.0% vs. placebo: 3.8%). The risk of worsening kidney parameters, especially within the first 4 weeks of treatment, is mentioned in section 4.4 and RMP to detail on the risk of eGFR and warn treating clinicians that a renal hemodynamic effect has been identified.

TEAE of gout was also observed more frequently in patients on acoramidis compared with the placebo group (11.2% vs. 8.1%). The applicant was also asked to explain this finding and discuss, whether inhibition of OAT1 by acoramidis could play a role, since SLC2A9 along with URAT1, OAT1 and OAT3 appear to be the main transporters regulating renal urate handling (Nigam et al., Curr Opin Nephrol Hypertens. 2018 Jul; 27(4): 305–313.). The higher number of gout events was included in section 4.8 of the SmPC as requested.

The applicant did not provide a complete tabulated list of adverse reactions in section 4.8 of the SmPC. Adverse events (AEs) occurring more frequently in the acoramidis group compared with placebo, especially if biologically plausible or a causal relationship cannot be excluded with certainty, should be listed in section 4.8 of the SmPC or well justified when it is not considered as ADR. For example, diarrhoea is mentioned in section 4.8 of the tafamidis SmPC as common adverse reaction and diarrhoea was also observed more frequently as TEAE in the acoramidis group (11.6%) vs. placebo (7.6%). Furthermore, two patients on acoramidis (0.5%) but no patient on placebo discontinued study treatment due to diarrhoea. In addition to diarrhoea other gastrointestinal disorders (nausea, abdominal discomfort and abdominal pain), rash, TEAEs of gout and cases of acute kidney injury (AEs and SAEs) were also numerically higher in the acoramidis treatment group compared with placebo and accompanied by creatinine increase and eGFR decrease.

Upon request, the applicant provided an analysis of the data of the events of diarrhoea, abdominal discomfort, abdominal pain, nausea, rash, gout and acute kidney injury. The review of the data concluded that there is insufficient evidence of a causal association between acoramidis and these events and that therefore, an update to the acoramidis SmPC Section 4.8 was considered not warranted at this time except for diarrhoea that was added to the table of adverse reactions in Section 4.8 with frequency: very common.

The evidence at this moment may not be sufficient to warrant a safety measure besides routine pharmacovigilance activities, but the applicant is expected to provide data on these adverse events in the first PSUR.

As requested, a discussion of GI events frequency in the ATTRm and ATTRwt population was provided. It was concluded that, overall, the incidence of TEAEs in the MedDRA Gastrointestinal disorders SOC was similar between the acoramidis and placebo groups in both patient subpopulations. Diarrhoea was more frequent in ATTRwt population treated with acoramidis than in placebo (n=44, 11.6% in acoramidis vs n=13, 6.8% in placebo), but in ATTRm was more common in placebo than acoramidis group (n=5, 12.2% in acoramidis vs n=3, 15% in placebo).

The presentation of proportions of adverse events in subgroups of ATTR may be misleading, given the considerable difference in sizes between these subgroups; rather, we prefer to focus on the overall acoramidis-treated group vs placebo. In that respect, there is a clear imbalance for diarrhoea (which is also a labelled common adverse reaction for tafamidis) and a clear imbalance in drug interruption or

withdrawal due to diarrhoea. It is possible to conclude that there is a reasonable possibility that diarrhoea is causally related to acoramidis and section 4.8 was updated accordingly as requested.

Phase 2 Study AG10-201

The most frequently reported TEAEs by PT were constipation (12.2% of all participants), diarrhoea (10.2%), muscle spasms (8.2%), and atrial fibrillation (8.2%).

Safety analyses across studies

In the Integrated Acoramidis Treatment - Studies AG10-202, AG10-301 and AG10304, the most common TEAEs (EAIRs > 30) were in the SOCs of infections and infestations, cardiac disorders and gastrointestinal disorders. The most common TEAEs (EAIRs > 10 overall) by PT were cardiac failure and COVID-19.

In the OLE Studies AG10-202 and AG10-304, the most commonly reported (> 20%) TEAEs were in the SOCs of infections and infestations, and cardiac disorders. The most common (> 10%) TEAE (by PT) was fall.

The applicant was requested to provide any new relevant safety data from the OLE study AG10 304 since the cut-off data 27 February 2023. As requested, the applicant provided a review of new safety data for OLE Study AG10-304 and Study AG10-202. No new relevant safety issues were identified, and so the safety profile is considered unchanged.

In the Integrated Acoramidis Treatment - Studies AG10-202, AG10-301 and AG10-304, the TEAEs considered by the Investigator to be related to acoramidis were reported with low incidence and EAIRs ≥ 0.5 overall by PT were reported for nausea (EAIR 0.6), diarrhoea (EAIR 0.5), and rash (EAIR 0.5).

In the OLE Studies AG10-202 and AG10-304, there were two treatment-related TEAEs by PT that were experienced by ≥ 2 participants overall in the OLE studies: diarrhoea in three participants (two participants in Study AG10-304 and one participant in Study AG10-202) and rash in two participants (one participant in each study).

The TEAEs most frequently reported were consistent with the known progression the disease, the cardiomyopathy and other comorbidities expected for this population. However, TEAEs in the SOC of gastrointestinal disorders (specially diarrhoea, nausea, abdominal discomfort and abdominal pain) and rash, consistently appears as a common TEAEs in the different studies and analysis. Although these symptoms and signals are often associated with the disease, there appears to be a statistically significant difference between the treatment group and placebo.

The most frequently reported serious TEAEs by PT (> 3% in either treatment group in Study AG10-301) included cardiac failure, cardiac failure acute, atrial fibrillation, acute kidney injury, fall, and COVID-19 pneumonia. In the acoramidis treatment group, serious TEAEs of cardiac failure acute in one participant and syncope and hypotension in a second participant were assessed by the Investigator as related to study drug. The SAE of cardiac failure acute in one participant occurred at the end of the 30-month study, 12 days after discontinuation of study treatment. The participant's underlying condition of ATTR-CM, including unstable angina, coronary artery disease, hypertension, atrial fibrillation, chronic systolic and diastolic heart failure, and ischemic cardiomyopathy provided likely aetiologies. The SAEs of hypotension and syncope in another participant had several likely aetiologies, including the use of concomitant medications with known hypotensive effect, underlying congestive heart failure, and the effect of environmental factors of extreme heat leading to dehydration. In both participants, the applicant assessed these SAEs as not related to study drug. This is acceptable.

Fall safety data were consistent with the aging patient population under study and no clinically meaningful imbalance in TEAEs or SAEs was observed between the treatment groups. The applicant

states that there was no evidence to establish a causal relationship between acoramidis and fall. This is acceptable.

Hepatic and renal safety data were consistent with the patient population under study. No participant had ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN or with a change of ALT or AST > 10 × ULN during routine scheduled laboratory evaluations.

Acoramidis has not been studied in patients with hepatic impairment. The clinical studies with acoramidis in patients with symptomatic ATTR-CM required ALT and AST ≤ 3 × ULN and total bilirubin ≤ 3 × ULN (≤ 2 × ULN in Phase 2 Study AG10-201) at Screening. The applicant provided a review and discussion of pharmacokinetic profile, safety profile, laboratory findings in study AG10-301 and overall postbaseline liver function tests. Patients with abnormal liver function tests at Screening, defined as ALT or AST > 3 × ULN or total bilirubin > 3 × ULN, were excluded from Study AG10-301. The safety profile analysis was focused in 10 patients (6 in the acoramidis group, 4 in the placebo group) that developed elevated hepatic enzymes (ALT or AST > 3 × ULN) after screening.

There were no clinically meaningful differences between treatment groups in TEAEs reported after development of elevated hepatic enzymes and there were no safety signals of clinical concern in this subset of study participants who developed elevated ALT or AST after Screening. The acoramidis PK profile was examined for 2 of the 6 participants and there is no evidence that PK values differ in patients with elevated hepatic enzymes. The applicant concluded that, based on currently available data, there are no safety issues with administering acoramidis in patients with mild hepatic enzyme abnormalities. However, there was no evidence that this analysis included patients with true hepatic impairment. It can only be stated that the 2 patients with PK assessment and liver enzymes up to 3x ULN but without bilirubin increase did not show concerns regarding different ACME pattern or safety issues. Of note, increased bilirubin without increase liver enzymes is common in the “normal” population, as > 7% of the healthy population may fulfil criteria for Gilbert’s syndrome.

Presently there is not sufficient information to support the use of acoramidis in hepatic impaired patients. Still, this aspect does not prevent the benefit-risk assessment in the overall population.

There are no data on the use of acoramidis in pregnant women. There are no available data on the presence of acoramidis in either human or animal milk or the effects of the drug on breastfed infants or maternal milk production. In Study AG10-001, there was one healthy adult participant who became pregnant while in the study. Repeated attempts to contact the participant for follow-up regarding pregnancy outcomes were unsuccessful. The applicant proposes the following update to SmPC Section 4.6 Fertility, pregnancy and lactation:

“It is unknown whether acoramidis or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Acoramidis should not be used during breastfeeding.” It is considered acceptable.

No drug-drug interaction was reported. The overall extent of absorption of acoramidis was not influenced by food.

2.6.10. Conclusions on the clinical safety

The safety of acoramidis has been studied in 12 clinical studies.

Key findings from the safety data of the pivotal Phase 3 study AG10-301 are as follows:

a) Acoramidis displayed a safety profile consistent with the disease under study and the co-morbidities expected for the target ATTR-CM study population (mean age of the patients was 77.3 ±6.6 years).

b) The frequency, type, and severity of TEAEs were similar in the acoramidis and placebo groups.

c) Serious adverse events (54.6% vs. 64.9%), TEAEs leading to hospitalisation (50.4% vs. 60.7%) and TEAEs with a fatal outcome (14.3% vs. 17.1%) were lower in patients on acoramidis vs. placebo.

d) Incidence of to TEAEs leading to study drug discontinuation was low and similar in both groups (acoramidis: 9.3%; placebo: 8.5%).

e) Findings from vital signs, ECG and physical examination were consistent with the patient population under study. Mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate were comparable in both treatment groups. The mean ECG intervals at baseline in both treatment groups were consistent and did not markedly change throughout the duration of the study.

f) There was no clinically meaningful difference in laboratory parameters (haematology and clinical chemistry) between treatment groups except for a slight increase in creatinine (approximately 15%) and decrease in eGFR (acoramidis: -8.2 mL/min and Placebo: -0.7 mL/min) which were most pronounced at day 28.

In conclusion: neither analysis of the pivotal nor of the data across all 12 studies raise major concerns regarding safety.

2.7. Risk Management Plan

The applicant provided RMP version 0.3 dated 6 November 2024.

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	*None*
Important potential risks	Reproductive and developmental toxicity Kidney injury
Missing information	*None*

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities were proposed. No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed.

It was considered that routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

It was considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

It was considered that the routine risk minimisation measures are sufficient to mitigate the safety concerns of the RMP.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
Reproductive and developmental toxicity	Routine risk minimisation measures: Relevant information is provided in SmPC Section 4.6 Fertility, pregnancy, and lactation; Section 5.3 Preclinical safety data; and in the Package leaflet: Information for patients, No. 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Kidney injury	Routine risk minimisation measures: Relevant information is provided in SmPC Section 4.4 Special warnings and precautions for use – Renal haemodynamic parameters; Section 5.1 Pharmacodynamic properties; and in the Package leaflet: Information for patients, No. 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The PRAC and the CHMP considers that the risk management plan version 0.3 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22 November 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Beyonttra (Acoramidis) is included in the additional monitoring list as:

It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease resulting from the deposition of misfolded TTR as amyloid fibrils in various organs, predominantly the nerves and heart (Castaño and Maurer, 2019; Ruberg et al., 2019). The most clinically important manifestations are the result of involvement of the peripheral nervous system and the heart. Accumulation of amyloid fibrils in the heart causes an infiltrative, restrictive cardiomyopathy (ATTR-CM) resulting in progressive clinical heart failure associated with high mortality and morbidity. Patients with ATTR-CM typically experience frequent hospitalisations for heart failure, irreversible loss of physical function, and worsening health status and QoL. Advanced ATTR-CM causes some of the most deleterious adverse clinical outcomes in ATTR (Castaño and Maurer, 2019; Ioannou et al., 2023; Ruberg et al., 2019).

The proposed indication is “for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy”.

3.1.2. Available therapies and unmet medical need

The cornerstone of the contemporary treatment of ATTR-CM is the careful management of volume status with diuretics (mainly loop diuretics, but also potent tubular diuretics like metolazone). Aldosterone receptor antagonists may be useful as they are effective diuretics with a mechanism that is complementary to that of loop diuretics. The use of afterload reduction with renin-angiotensin antagonists (angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers, neutral endopeptidase inhibitors) and neurohormonal modulators (chronic, high dose beta blockade) are often poorly tolerated due to the restrictive physiology of infiltrative cardiomyopathy. Digoxin or calcium channel blockers are generally avoided in the management of ATTR-CM. Patients with ATTR-CM are at high risk for the concomitant development of atrial fibrillation requiring both pharmacological and non-pharmacological interventions, as well as systemic anticoagulation for optimal clinical management.

Currently, tafamidis is the only targeted therapy approved for the treatment of ATTR-CM in the EU. The other therapy in clinical use for the treatment of ATTR-CM is diflunisal, a nonselective COX inhibitor developed as a nonsteroidal anti-inflammatory drug that has TTR stabilizing activity. It is used off-label and it is not widely marketed.

Despite this important therapeutic advance, a substantial medical need persists. In the tafamidis study ATTR-ACT, about 30% of patients died in the combined active treatment arms, and the annualised rate of CV-related hospitalisation remained high at 0.48/year, with a benefit of tafamidis on CV-related hospitalisation emerging only after 9 months. In a recently conducted, 12-month clinical study of the TTR knockdown agent patisiran, concomitant use of open-label tafamidis was frequent, and the incidence of progression on tafamidis was substantial, with 22% of patients who were on tafamidis alone (i.e., in the placebo arm relative to patisiran) showing worsening of heart failure by NYHA class after 12 months.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicentre, randomised, placebo-controlled study comparing acoramidis (n=409) vs. placebo (n=202) in symptomatic ATTRv or ATTRwt cardiomyopathy adult patients with or without addition of tafamidis after 12 months of treatment.

3.2. Favourable effects

The primary endpoint of the above study (win ratio analysis for hierarchical combination of all-cause mortality, cv-related hospitalisation, change from baseline in NT-proBNP and change from baseline in 6MWD, mITT population) was met. The win ratio for the pre-specified primary analysis was 1.772 (96% CI: 1.402, 2.240), indicating that an acoramidis-treated participant had a 77.2% higher chance of deriving a treatment benefit than a placebo-treated participant.

Acoramidis delayed the first occurrence of CV-related hospitalisation in comparison to placebo. A clinically relevant treatment effect was observed for acoramidis compared to placebo (hazard ratio: 0.601, stratified Cox proportional hazard model; 95% CI: 0.451, 0.800; nominal p value = 0.0005).

For the combination of all-cause mortality and CV-related hospitalisations over a 30-month period, numerically, statistical significance was achieved on the hierarchical two-component (all-cause mortality and frequency of CV-related hospitalisations) F-S test, indicating a superior treatment effect of acoramidis compared to placebo. The win ratio (95% CI) was 1.464 (1.067, 2.009), nominal p = 0.0182

The composite of time-to-first-event of all-cause mortality or CV-related hospitalisation was reported in 147 (35.9%) and 102 (50.5%) acoramidis and placebo-treated participants, respectively, corresponding to a 14.6% absolute risk reduction. A 35.5% hazard reduction in all-cause mortality or first CV-related hospitalisation at month 30 was observed in the acoramidis treatment group compared to placebo (hazard ratio: 0.645 [95% CI: 0.500, 0.832; nominal p = 0.0008]. The difference was mainly driven by first CV hospitalisations.

A treatment effect for change from baseline in 6MWD favouring acoramidis was observed, with the curves starting to separate at month 18, and with separation increasing in magnitude through month 30. At month 30, a statistically significant ($p < 0.0001$) and clinically meaningful treatment effect on 6MWD was observed favouring acoramidis, with 40 meters LS mean difference between treatment groups in change from baseline.

At month 30, the observed mean KCCQ-OS scores were 71 and 64 in the acoramidis and placebo groups, respectively. The observed mean (percent) changes from baseline in KCCQ-OS score at month 30 were -3.1 (-3.0%) and -10.8 (-14.0%) in the acoramidis and placebo groups, respectively.

3.3. Uncertainties and limitations about favourable effects

Several amendments were made on the definition of the primary and secondary endpoints while the study was ongoing. Amendment 5 included 6-MWD as an additional component, Amendment 6 change from baseline in NT-proBNP as an additional component to be analysed in the hierarchical testing procedure. The applicant has provided the analyses with the original primary endpoint, which were considered acceptable.

The finally implemented primary endpoint was not considered acceptable. These key endpoints were considered based on the nominal p-values provided, and additional analyses for the dual endpoints was provided in order to further analyse the robustness of these results. Mainly, analyses in the ITT (as opposed to the proposed mITT population) was provided for all relevant endpoints.

Subgroup analyses

Overall, the results on efficacy were consistent for most subgroups with the exception of NYHA class III. For the primary 4-fold efficacy endpoint and for the 6-MWD, HRs did not indicate efficacy in patients with NYHA III and only limited efficacy was observed for the cumulative frequency of CV hospitalisations. For all-cause mortality, the point estimate of the HRs was even in favour of placebo with an early shift favouring placebo around month 12 which is reversed by month 19. The latter finding was further analysed and the Kaplan - Meier curves for mortality by NYHA category were provided. The data consistently indicate lower efficacy in patients at NYHA stage III and NAC ATTR stage III as compared to patients at earlier stages or the disease. As an example, there was no benefit for ACM or First CVH. A continuous trend to lower efficacy was consistent when comparing NYHA I over II to III. Section 5.1 of SmPC clearly identifies the lower response of NYHA Class III patients as compared to the other classes.

Considering that also data available for tafamidis indicated a lower efficacy in patients with NYHA III (Maurer et al., 2018) the results may indeed indicate a lower efficacy of TTR stabilisers in advanced stages of the disease.

3.4. Unfavourable effects

Gastrointestinal adverse events were very frequent, more so in the acoramidis group. This is of concern given the frailty of the patients.

3.5. Uncertainties and limitations about unfavourable effects

The major uncertainties and limitations about unfavourable effects of acoramidis are related to kidney parameters and renal function.

Although the evidence regarding patients who worsen eGFR does not readily point to clear nephrotoxicity, and that those patients who worsen renal function and do not improve with treatment stop seem similar in frequency and characteristics between treatment arms, on clinical grounds at the moment one cannot clearly exclude the risk of nephrotoxicity, especially if the patient has a disease related risk for developing renal insufficiency and is chronically hypotensive. Therefore, section 4.4 of the SmPC and the RMP were updated to detail on the risk of eGFR and to warn treating clinicians that a renal haemodynamic effect has been identified.

There is a clear imbalance for diarrhoea and a clear imbalance in drug interruption or withdrawal due to diarrhoea. It is concluded that there is a reasonable possibility that diarrhoea is causally related to acoramidis. This is reflected in section 4.8 of the SmPC.

TEAE of gout was also observed more frequently in patients on acoramidis compared with the placebo group (11.2% vs. 8.1%). The applicant was asked to explain this finding and discuss, whether inhibition of OAT1 by acoramidis could play a role, since SLC2A9 along with URAT1, OAT1 and OAT3 appear to be the main transporters regulating renal urate handling (Nigam et al., Curr Opin Nephrol Hypertens. 2018 Jul; 27(4): 305–313.). The higher number of gout events has been also reflected in section 4.8 of the SmPC.

Given the clear growth of the duration of child birth potential among women, and the progressive older age at which women give birth, it is not particularly unlikely that women with ATTR-CM may become pregnant; furthermore, becoming pregnant or medically interrupting pregnancy carries risks in the ATTR-CM population. Facing this reproductive and developmental toxicity was added to the approved version of the RMP as an important potential risk.

Related with concerns on renal effects and following PRAC recommendation, the applicant updated the RMP to include kidney injury as an important potential risk in the summary of safety concerns of the RMP.

3.6. Effects table

Table 27: Effects table for Beyonttra

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
F-S at month 30	Finkelstein-Schoenfeld Win Ratio Analysis for Hierarchical Combination of All-cause Mortality, CV-related Hospitalisation, Change from Baseline in NT-proBNP and Change from Baseline in 6MWD	Wins	18,346	10,351	Choice of the F-S hierarchical combination with added 6MWD and NT-proBNP. Win ratio (vs placebo): 1.772; 96% CI of Win Ratio (1.402-2.240), based on mITT but not on ITT	Study AG10-301
Mortality at month 30	All-cause Mortality death rate	%	19.3%	25.7%	The studied population may not be thoroughly extrapolated. No NYHA class discussion A difference of 6.4% in mortality in a rapidly progressive disease, based on mITT but not on ITT	Study AG10-301
6MWD at month 30	Change from baseline in 6MWD	meters	366	322	6MWD as a marker for cardiomyopathy treatment response A 40 m average difference between groups may be relevant for autonomy range, based on mITT but not on ITT	Study AG10-301
KCCQ-OS at month 30	Change from baseline in KCCQ-OS	Point score difference (%)	-3.1 (-3.0%)	-10.8 (-14.0%)	Clinical relevance of the 7.7 point difference	Study AG10-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
F-S at month 30 dual	Finkelstein-Schoenfeld Win Ratio Analysis for Hierarchical Combination of All-cause Mortality, CV-related Hospitalisation,	Wins	9918	6774	Not included in the confirmatory testing strategy, Win ratio vs. placebo (95% CI): 1.464 (1.067, 2.009), nominal p = 0.0182 based on mITT but not on ITT	Study AG10-301
First event all-cause mortality/ CV-related Hospitalisation	Time to All-cause Mortality or First CV-related Hospitalisation	Events (%)	147 (35.9%)	102 (50.5%)	HR 0.645 [95% CI: 0.500, 0.832; nominal p = 0.0008. Not included in the confirmatory testing strategy, based on mITT but not on ITT	Study AG10-301
Unfavourable Effects						
Any treatment-emergent adverse events (TEAEs)	TEAE (n [%])		413 (98.1%)	206 (97.6%)		Study AG10-301, Safety Population
TEAE with fatal outcome	TEAE (n [%])		60 (14.3%)	36 (17.1%)		Study AG10-301, Safety Population
TEAE leading to hospitalisation	TEAE (n [%])		212 (50.4%)	128 (60.7%)		Study AG10-301, Safety Population
TEAE leading to study drug discontinuation	TEAE (n [%])		39 (9.3%)	18 (8.5%)		Study AG10-301, Safety Population
Gout	TEAE (n [%])		47 (11.2%)	17 (8.1%)		Study AG10-301, Safety Population
Diarrhoea	TEAE (n [%])		49 (11.6%)	16 (7.6%)		Study AG10-301, Safety Population
Nausea	Incidence of nausea	%	1.4	0.5	GI events may be especially troublesome in this frail population	Study AG10-301 Safety population

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Abdominal discomfort	Incidence of Abdominal discomfort	%	0.7	0.0	GI events may be especially troublesome in this frail population	Study AG10-301 Safety population
Any treatment-emergent serious adverse events (SAEs)	SAE (n [%])		230 (54.6%)	137 (64.9%)		Study AG10-301, Safety Population
Cardiac failure	SAE (n [%])		45 (10.7%)	39 (18.5%)		Study AG10-301, Safety Population
Cardiac failure acute	SAE (n [%])		21 (5.0%)	14 (6.6%)		Study AG10-301, Safety Population
Atrial fibrillation	SAE (n [%])		19 (4.5%)	15 (7.1%)		Study AG10-301, Safety Population
Acute kidney injury	SAE (n [%])		21 (5.0%)	8 (3.8%)		Study AG10-301, Safety Population

Abbreviations:

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

ATTR cardiomyopathy is a rapid progressive lethal disease. For ATTRv diseases, several treatments have been made available in the last 5 years, and the field is rapidly growing. Acoramidis is the second in a row TTR stabiliser to be administered in patients with ATTR cardiomyopathy, a disease with high medical need due to high morbidity and mortality. As such, a new agent for the treatment of ATTR cardiomyopathy is still a need.

The endpoints considered most important for the assessment covering mortality and hospitalisation for CV events showed a clinically relevant and nominally statistically significant benefit, mainly due to a reduction in CV hospitalisation. The result is accompanied by a small to moderate benefit in quality of life as assessed by KCCQ and a clinically relevant benefit on functional capacity at month 30 as assessed by the 6 MWD. Efficacy of acoramidis in patients with ATTR cardiomyopathy was assessed in the absence of treatment of medicinal products produced based on siRNA/ASO technology that have

been approved for ATTR polyneuropathy but that have shown at least in part to have also some cardiovascular benefit in the first 12 months of treatment in the absence of tafamidis. Therefore, a clinically relevant benefit has not been demonstrated in an add-on therapy.

There was a time delay for some of the endpoints investigated. Whereas a beneficial effect on CV hospitalisation and on KCCQ was observed early after treatment initiation, a benefit on functional capacity (6-MWT) or a numerical benefit on all-cause mortality took several months to appear. This is not unexpected and similar to what has been observed with other TTR stabilisers (tafamidis) in the past.

Efficacy can be considered established at earlier stage of the disease although, despite the lack of study power for the NYHA class III population, the data provided consistency signs of this population to be lower benefiters. Similar to another approved amyloid stabiliser agents, this lower efficacy was reflected in section 5.1 of the SmPC. As per the inclusion criteria, efficacy has only been demonstrated in symptomatic patients and this was reflected as well in section 5.1 of the SmPC. In addition, it should be also highlighted in section 5.1 that a lower response of NYHA Class III patients is observed as compared to the other classes.

Unfavourable effects

Acoramidis displayed a safety profile consistent with the disease under study and the co-morbidities expected for the target ATTR-CM study population. The overall frequency, type, and severity of TEAEs were similar in the acoramidis and placebo treatment groups. Fewer serious adverse events (54.6% vs. 64.9%), TEAEs leading to hospitalisation (50.4% vs. 60.7%) and TEAEs with a fatal outcome (14.3% vs. 17.1%) were reported for acoramidis compared with placebo.

The major uncertainties and limitations about unfavourable effects of acoramidis related to kidney parameters and renal function are reflected in the SmPC.

There is an imbalance for diarrhoea and an imbalance in drug interruption or withdrawal due to diarrhoea, as such there is a reasonable possibility that diarrhoea is causally related to acoramidis. TEAE of gout was also observed more frequently in patients on acoramidis compared with the placebo group (11.2% vs. 8.1%).

3.7.2. Balance of benefits and risks

All patients had symptomatic disease at the time of randomisation as suggested by the inclusion criterion „NYHA Class I-III symptoms due to ATTR-CM“. This has been appropriately reflected in section 5.1 of the SmPC. In addition, it has also been highlighted in this section that a lower response of NYHA Class III patients was observed as compared to the other classes.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Beyonttra is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Beyonttra is not similar to Vyndaqel, Tegsedi, Onpattro, Amvuttra, Wainuza within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Beyonttra is favourable in the following indication(s):

Beyonttra is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product on medical prescription for renewable or non-renewable delivery.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that acoramidis is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.