EU Risk Management Plan
for
BEYONTTRA 356 mg

Film-coated tablets

Data Lock Point: 31AUG2023

RMP Version Number	0.3
Data Lock Point for this RMP	31AUG2023
Date of Final Sign Off	06NOV2024
Rationale for Submitting an Updated RMP	*N/A – initial marketing authorisation application*
Summary of Significant Changes in this RMP	*N/A – initial marketing authorisation application*

EEA QPPV:	Susanne Becker
Signature / Date:	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
ACE	Angiotensin converting enzyme
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AG	Acylglucuronide
AKI	Acute kidney injury
ALT	Alanine Aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATTR	Transthyretin Amyloidosis
ATTR-CM	Transthyretin Amyloidosis with Cardiomyopathy
ATTRm	ATTR associated with mutants
ATTRv	Variant ATTR
ATTRwt	Wild type ATTR
AUC	Area Under the Concentration-Time Curve
$AUC_{0\text{-}24h}$	AUC from 0 to 24 hours after last dose
BE	Bioequivalence
BID	Twice daily
CKD	Chronic kidney disease
C_{max}	Maximum Concentration
CNS	Central Nervous System
CV	Cardiovascular
CVH	Cardiovascular Related Hospitalisation
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-foetal Development
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GLP	Good Laboratory Practice
hERG	human Ether-a-go-go-Related Gene
ICH	International Council for Harmonisation
INN	International Nonproprietary Names
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum Recommended Human Dose

NOAEL	No-Observed-Adverse-Effect-Level
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Pharmacodynamics
PK	Pharmacokinetics
PPND	Pre- and postnatal developmental
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QoL	Quality of Life
RMP	Risk Management Plan
SD	Sprague-Dawley
SGLT-2	Sodium-glucose cotransporter 2
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TTR	Transthyretin
TTRv	Variant Transthyretin
TTRwt	Wild Type Transthyretin
UACR	Urine albumin-to-creatinine ratio
ULN	Upper Limit of Normal
US	United States

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active Substance (INN or common name)	Acoramidis
Pharmacotherapeutic Group (ATC Code)	C01EB25
Marketing Authorisation Applicant	**BridgeBio Europe B.V.** Weerdestein 97 Amsterdam, Netherlands 1083 GG
Medicinal Products to which this RMP Refers	1
Invented name(s) in the European Economic Area (EEA)	BEYONTTRA
Marketing Authorisation Procedure	Centralised
Brief Description of the Product	*Chemical class:* Acoramidis is a specific stabiliser of transthyretin (TTR).
	Summary of mode of action: Acoramidis was designed to mimic the disease protective genetic variant (T119M), through the formation of hydrogen bonds with adjacent serine residues within both thyroxine binding sites of the tetramer. This interaction enhances the stability of the tetramer, inhibiting its dissociation into monomers, thus slowing the amyloidogenic process that results in Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM).
	Important information about its composition: No relevant information.
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)
Indication in the EEA	BEYONTTRA is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
	Proposed: Not applicable – This is an initial marketing authorisation application.

Dosage in the EEA	The recommended dose of acoramidis is 712 mg (two tablets, 356 mg) orally, twice daily, corresponding to a total daily dose of 1424 mg.
	Proposed: N/A – initial marketing authorisation application
Pharmaceutical Form and Strengths	Pharmaceutical form: Film-coated tablets. 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 Strength: Each film-coated tablet contains acoramidis hydrochloride equivalent to 356 mg acoramidis.
Is/will the product be subject to additional monitoring in the EU?	*Yes*

PART II: SAFETY SPECIFICATION

MODULE SI Epidemiology of the Indication and Target Population

Indication

Acoramidis is indicated in the EEA for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Transthyretin amyloidosis (ATTR) is a rare, multisystem, progressive, debilitating, and ultimately fatal disease resulting from the deposition of misfolded transthyretin (TTR) as amyloid fibrils in various organs, predominantly the nerves and heart. Cardiac involvement (ATTR-CM) determines the adverse clinical outcomes in ATTR amyloidosis (Castaño and Maurer 2019, Ruberg et al. 2019).

Incidence

The ATTR-CM disease landscape has undergone a transformation 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 AL amyloidosis by serum and urine protein biochemistry (Castano et al. 2016, Gillmore et al. 2016); (2) a widespread, global engagement by professional societies (Maurer et al. 2019, Fine et al. 2020, Kitaoka et al. 2020, Garcia-Pavia et al. 2021a, Garcia-Pavia et al. 2021b, Yilmaz et al. 2021, Kittleson et al. 2023), and advocacy organizations to raise awareness among cardiologists and the broader medical community that 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 (Fosbol et al. 2019, Westin et al. 2020).

Prevalence

Europe

The estimated prevalence of ATTR in Europe is 4.2 per 10,000 individuals (as further described in the EU Orphan Drug Designation (ODD) maintenance report).

Worldwide

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 noninvasive 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 (Gonzalez-Lopez et al. 2015, Aimo et al. 2022, Merlo et al. 2022).

Demographics of the Population in the Proposed Indication – age, gender, racial and/or ethnic origin and risk factors for the disease

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 the 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 (Garcia-Pavia et al. 2021b, Kittleson et al. 2023).

Existing Treatment Options

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.

The cornerstone of the contemporary treatment of ATTR-CM is 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 (ARBs), 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, Vyndaqel (tafamidis) is the only targeted therapy approved for the treatment of ATTR-CM in the EEA (Vyndaqel-EPAR 2019), United States (US) (Vyndaqel-FDA-CDER 2019) and many other countries world-wide. Tafamidis is a small molecule that binds and stabilises the TTR tetramer. Another 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 stabilising 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.

Mortality and Morbidity

Advanced ATTR-CM causes some of the most deleterious adverse clinical outcomes in ATTR (Castaño and Maurer 2019, Ruberg et al. 2019, Ioannou et al. 2023). In the tafamidis ATTR-ACT study (a 30-month, randomised, double-blind, placebo-controlled study conducted in patients with ATTR-CM)(Maurer et al. 2018), 43% of participants died in the placebo arm, making untreated ATTR-CM more deadly than lung cancer and about two times more deadly than otherwise undifferentiated heart failure (Lauppe et al. 2022).

Despite increased awareness and advances in diagnostic modalities, ATTR-CM remains an important, under-recognised cause of heart failure leading to excess mortality, cardiovascular (CV) morbidity, impaired physical function, and reduced quality of life (QoL). In particular, cardiac involvement is associated with worse prognosis (median survival of 2 to 5 years) (Ioannou et al. 2022).

Important Co-morbidities

Patients diagnosed with ATTR-CM tend to be male, on average 60 years old or older, and present with heart failure and preserved ejection fraction, often with cardiac conduction abnormalities (varying degrees of heart block) on the 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 (Garcia-Pavia et al. 2021b, Kittleson et al. 2023). TTR gene variants have been identified that are transmitted in an autosomal dominant fashion (Arno and Cowger 2022, Obi et al. 2022). V122I is the most common pathogenic variant found in the US, affecting 3-4% of Black Americans, with a variable documented penetrance and clinical expressivity (Agbor-Etang et al. 2021) (i.e., not all carriers appear to develop clinical manifestations). The mutation worldwide mapping has been published (Obi et al. 2022); the mutations V30M, I68L, T60A and L111M are the most common in European countries such as Portugal, Spain, France, Germany, Sweden, Ireland, Italy, and Denmark. However, V30M is the variant that is more present among these European countries. The results from 14-year update of the Transthyretin Amyloidosis Outcomes Survey (THAOS) database show that V30M is the most prevalent genotype (49.6% worldwide and 64.6% in Europe) (Dispenzieri et al. 2022). The V30M pathogenic variant was the first to be described and is most commonly found in three geographic locations, demonstrating a founder effect. It was initially described in the Portuguese in 1952 as Familial Amyloid Polyneuropathy and subsequently in unrelated populations in Sweden and Japan (Soares et al. 2005). Also first described in Portugal was a stabilising variant (T119M) that protects V30M carriers (compound heterozygotes) from either developing or progressing the otherwise rapidly progressive polyneuropathy associated with V30M carriage (Almeida et al. 2000).

Because of the age-dependent development of ATTR-CM, many patients have true comorbid conditions including hypertension, diabetes mellitus, ischaemic heart disease, or aortic stenosis (particularly low flow-low gradient) before amyloidosis develops. Depending on the mutation, patients with ATTR-CM show common signs and symptoms of heart failure, such as dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, oedema, fatigue, exercise intolerance, dizziness/syncope, palpitations, electrical conduction abnormalities, and arrhythmias (Maurer et al. 2019).

MODULE SII Non-clinical Part of the Safety Specification

Non-Clinical Programme Overview

The completed nonclinical studies were intended to support the development and registration of acoramidis for the treatment of TTR amyloidosis in adult patients with cardiomyopathy and were consistent with the requirements of International Council for Harmonisation "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (ICH M3[R2] 2009).

The totality of the nonclinical data indicates safety margins relative to human therapeutic exposures of acoramidis and low potential for adverse effects at anticipated therapeutics exposures.

Pharmacokinetics

The metabolism of acoramidis in rat and dog hepatocytes was determined to be qualitatively comparable to that in human hepatocytes; the rat and dog were chosen as the toxicologically relevant species. The formation of the primary metabolite acoramidis-β-D-glucuronide (acoramidis acylglucuronide [acoramidis-AG] in vivo was confirmed by quantification of acoramidis-AG in plasma of rats, dogs, and humans (Table 2; study AG10-007).

The nonclinical pharmacokinetics of acoramidis were characterised by low clearance and volume of distribution in mice, rats, dogs, and monkeys. After oral administration, absorption was rapid in all species. After repeated oral administration, systemic exposure to acoramidis increased generally in a dose proportional manner in rats and in dogs.

Metabolism

The comparative biotransformation pathways between animals and humans demonstrated using both in-vitro and in-vivo systems demonstrated the predominant pathway was glucuronidation, with other pathways such as oxidation, desaturation and conjugation playing a minor role. The metabolites detected in humans were observed in at least one of the nonclinical species (rat or dog).

Excretion

In rats and dogs, [^{14}C] acoramidis-derived radioactivity was rapidly absorbed and eliminated (> 95% recovered) after oral administration. Faecal excretion was the main excretory pathway in rats (79.0% dose in male and 71.7% dose in female) and in dogs (51.0% dose in male and 66.0% of dose in female). Urinary excretion for rats was 16.3-24.8% of dose whereas in dogs, it ranged from 27.8-34.4% of dose. Biliary excretion was 80.5% of dose in rats. Biliary excretion of direct acylglucuronides (M1, M2, M3, M4 and M7) accounted for 67.2% of dose in rats; this coupled with the low abundance of acoramidis in bile and urine indicates that the hepatic metabolism is the primary mechanism of elimination of acoramidis.

Toxicology

Acoramidis was assessed extensively in a series of Good Laboratory Practices (GLP)-compliant repeat-dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicity, and phototoxicity studies (Table 2). Safety margins based on C_{max} and area under the concentration-time curve (AUC) confirmed that the exposure of the metabolite achieved in the toxicology species was sufficient to cover that observed in humans (safety margins of 12 and 16 from the 26-week rat study and 19 and 26 from the 9-month dog study, based on C_{max} and AUC, respectively).

In vitro metabolite profiling with rat, dog, monkey, and human hepatocyte incubations indicated that acoramidis-β-D-glucuronide (acoramidis acylglucuronide [acoramidis-AG]) was the predominant metabolite across all species after a 4-hour incubation. There were no unique human metabolites observed.

Since the metabolism of acoramidis in rat and dog hepatocytes was qualitatively comparable to that in human hepatocytes, the rat and dog were chosen as the toxicologically relevant species. The formation of acoramidis-AG in vivo has been confirmed by quantification of acoramidis-AG in plasma of rats, dogs, and humans.

Repeated Dose Toxicity

Repeat dose toxicity and toxicokinetics were assessed in 9 studies ranging from 7 days to 39 weeks in rats and dogs (Table 2). In the 39-week repeat-dose studies in dogs the mean C_{max} and AUC at No-Observed-Adverse-Effect-Level (NOAEL) of 250 mg/kg/day was more than 18- to 25-fold higher than the C_{max} and AUC observed in healthy adult volunteers at steady state at 800 mg q12h. In the corresponding 26-week rat study, the NOAEL C_{max} and AUC provided a safety margin of 25- to 33-fold.

Genotoxicity

Acoramidis was negative for genotoxic findings suggesting there is a low risk of genotoxic injury to human subjects (Table 2). The genotoxic potential of acoramidis was assessed in accordance with International Council for Harmonisation (ICH) Guideline (ICH S2[R1] 2012) in one in vitro (bacterial reverse mutation assay) and two in vivo studies in rats (micronucleus and alkaline comet assay). These studies were negative for genotoxic findings suggesting there is a low risk of genotoxic injury to human subjects.

Reproductive and Developmental Toxicity

Acoramidis was evaluated in a complete nonclinical developmental and reproductive toxicity programme necessary to support human clinical trials and marketing authorisation in line with ICH Guideline (ICH S5[R3] 2020) and included a Segment I fertility and early embryonic development study in rats (Study 20143873), Segment II embryo-foetal development (EFD) studies in rat and rabbit (Study 8411734, Study 8411735), and Segment III pre- and postnatal developmental (PPND) toxicity study in rats (Study 8411736).

In the rat fertility study, NOEL (paternal and maternal) for reproductive toxicity was established at 1000 mg/kg/day, the highest tested dose and acoramidis had no effects on mating and fertility in either males or females, or on early embryonic survival.

In the EFD studies in rats and rabbits, no acoramidis-related adverse effects were observed on embryo-foetal viability. The NOAEL in embryo-foetal development studies in rats and rabbits were established at the highest tested dose of 1000 mg/kg/day acoramidis HCl and 200 mg/kg/day acoramidis HCl, respectively (approximatively 80 and 30 times, respectively, of the projected human dose/AUC/concentration). Consequently, the Sponsor considers that the safety relative to teratogenicity of the product is sufficiently demonstrated in this patient population.

In the PPND study in rats, no acoramidis-related effect was noted for any parameter during lactation for any dose group. F1 animals from litters of F0 animals administered the highest dose of 1000 mg/kg/day were noted with adverse, reduced mean body weights, which persisted after weaning but gained a comparable amount of weight to controls starting approximately 2 weeks into the maturation phase. Adverse, acoramidis-related effects on proximal and spatial learning were noted the highest dose of 1000 mg/kg/day. F1 animals at

350 mg/kg/day also were noted with acoramidis-related learning deficits; however, they were not considered adverse. 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 potential impact of adverse reduced body weight/body weight gain and food consumption in the F0 animals at 1000 mg/kg/day in both the EFD study and the PPND study confounds interpretation of the findings in this dose group in the studies. Based on the results of this study, the NOAEL for F0 maternal animals and prenatal and postnatal development was established at dose 350 mg/kg/day acoramidis HCl (approximatively 21 times the human exposure [AUC]) at the clinical dose of acoramidis.

These animal studies do not indicate impairment of fertility and direct harmful effects with respect to reproductive toxicity. Based on the reproductive toxicology data for acoramidis to date, the overall benefit-risk relationship for the target patient population of women of childbearing potential with ATTR was considered. There is no suspicion of human teratogenicity/genotoxicity based on genotoxic potential and nonclinical reproductive toxicity studies of relevance for early human pregnancy.

The adverse acoramidis-related effects of proximal and spatial learning in PPND studies in rats were at the highest dose of 1000 mg/kg/day, with safety margins of approximately 80 times of projected human dose/AUC/concentration. While this is well above the ICH threshold for concern, and the risk of injury to exposed women in pregnancy and their child is low, as a precautionary measure, it is preferable to avoid the use of acoramidis during pregnancy.

Carcinogenicity

The carcinogenicity programme included a pre-carcinogenicity study in mice, 26-week carcinogenicity study in transgenic mice, and 104-week carcinogenicity in rats. The 26-week mouse study was completed without any acoramidis-related neoplasms, organ weight effects, mortality, macroscopic or microscopic findings. Therefore, no carcinogenic potential was observed for acoramidis. In the 104-week rat study, no evidence of acoramidis-related mortality or effects on survival, clinical observations, body weight, food consumption, and neoplastic microscopic findings were noted. A sufficient number of animals survived to adequately evaluate the carcinogenic potential of acoramidis. The neoplastic NOAEL for acoramidis were the highest dose levels evaluated in both genders. In conclusion, acoramidis did not show any carcinogenic potential in either gender.

Phototoxicity

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.

Table 2: Acoramidis Summary of Non-Clinical Toxicology Programme

Study Type and Duration	GLP	Route of Administration	Species	Study Number
Repeated-Dose Toxicity – Module 4.2.3.2				
A 7-day Repeat-dose Toxicity and Toxicokinetic Study in Rats Administered AG10 Once Daily by Oral Gavage	No	Oral gavage	Rat	8355817
A 4-week Toxicity and Toxicokinetics Study in Rats Administered AG10 Once Daily by Oral Gavage with a 2-week Recovery Phase	Yes	Oral gavage	Rat	8355824
A 13-week Toxicity and Toxicokinetic Study in Rats Administered AG10 Once Daily by Oral Gavage with a 2-week Recovery Phase	Yes	Oral gavage	Rat	8366846
A 26-week Study of AG10 by Oral Gavage in Rats with a 28-day Recovery Period	Yes	Oral gavage	Rat	20141689
A 7-day Repeat-dose Toxicity and Toxicokinetic Study in Dogs Administered AG10 Once Daily by Oral Gavage with a 7-day Recovery	No	Oral gavage	Dog	8350153
A 7-day Repeat-dose Toxicity and Toxicokinetic Study in Dogs Administered AG10 Once Daily by Oral Gavage	No	Oral gavage	Dog	8355818
A 4-week Toxicity and Toxicokinetics Study in Dogs Administered AG10 Once Daily by Oral Gavage with 2-week Recovery Phase	Yes	Oral gavage	Dog	8355825
A 13-week Toxicity and Toxicokinetics Study in Dogs Administered AG10 Once Daily by Oral Gavage with a 2-week Recovery Phase	Yes	Oral gavage	Dog	8366847
A 39-week Study of AG10 by Oral Gavage in Dogs with a 28-day Recovery Period	Yes	Oral gavage	Dog	20141692
Genotoxicity Studies (In Vitro) – Module 4.2.3.3.1				
AG10: Bacterial Reverse Mutation Assay	Yes	In vitro	*Salmonella typhimurium*	8358481
Genotoxicity Studies (In Vivo) – Module 4.2.3.3.2				
AG10: Rat Micronucleus and Alkaline Comet Assay	Yes	Oral gavage	Rat	8358482
Carcinogenicity Studies (Long-term) – Module 4.2.3.4.1				
26-week Oral Gavage Carcinogenicity Study with AG10 in 001178-T (Hemizygous) mice	Yes	Oral gavage	Mouse	8410991
AG10: 104-week Oral Gavage Carcinogenicity and Toxicokinetic Study in Sprague Dawley Rats	Yes	Oral gavage	Rat	8409782
Carcinogenicity Studies (Short- or Medium-term) – Module 4.2.3.4.2				
AG10: Pre-carcinogenicity 4-week Oral Gavage Dose Range-Finding Toxicity and Toxicokinetic Study in Mice (CByB6F1-Tg[HRAS]2Jic: Wild Type)	No	Oral gavage	Mouse	8409781

Study Type and Duration	GLP	Route of Administration	Species	Study Number
Fertility and Early Embryonic Development – Module 4.2.3.5.1				
A Fertility and Early Embryonic Development Study of AG10 Administered by Oral (Gavage) in Rats	Yes	Oral gavage	Rat	20143873
Embryo-Fetal Development – Module 4.2.3.5.2				
Oral Gavage Dose Range-Finding Embryo-Fetal Developmental Study with AG10 in Rats	No	Oral gavage	Rat	8405806
Oral Gavage Embryo-Fetal Development and Toxicokinetics Study with AG10 in Rats	Yes	Oral gavage	Rat	8411734
Oral Gavage Dose Range-Finding Embryo-Fetal Developmental Study with AG10 in Rabbits	No	Oral gavage	Rabbit	8405805
Oral Gavage Embryo-Fetal Developmental and Toxicokinetic Study with AG10 in Rabbits	Yes	Oral gavage	Rabbit	8411735
Prenatal and Postnatal Development, including Maternal Function – Module 4.2.3.5.3				
Oral Gavage Study for Effects on Prenatal and Postnatal Development, Including Maternal Function, with AG10 in Rats	Yes	Oral gavage	Rat	8411736
Other Toxicity Studies (Phototoxicity) – Module 4.2.3.7				
Neutral Red Uptake Phototoxicity Assay of AG10 in BALB/c 3T3 Mouse Fibroblasts	Yes	In vitro	BALB/c 3T3 Mouse Fibroblasts	20128057

Source: Module 2.6.6, Table 1

Safety Pharmacology

Safety margins were calculated from toxicology studies using human exposure PK parameters (C_{max} and AUC) from two clinical studies (AG10-001, AG10-005). The data demonstrate that the acoramidis toxicology programme has established a wide safety margin and low potential for adverse effects at anticipated therapeutic exposures.

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.

In vitro and in vivo (rat and dog) safety pharmacology studies investigated the potential effect of acoramidis in the respiratory, central nervous and cardiovascular systems. In vitro (human ether-à-go-go-related gene (hERG) and safety panel) and in vivo (dog telemetry) experiments exclude relevant cardiac repolarisation effects at target therapeutic concentrations of acoramidis. These data suggest that acoramidis can be safely dosed to human subjects with low risk of affecting central nervous system, respiratory, or cardiovascular function.

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.

Respiratory safety pharmacology was evaluated (8355819) in doses of 100, 300, 1000 mg/kg in rats. No acoramidis related effects were observed in death, clinical observations, respiratory functions.

Central nervous system (CNS) safety studies (8355820) were conducted with a single dose of 100, 300 up to 1000 mg/kg. No observed effect level (NOEL) at 10000 mg/kg was reached after one dose.

Cardiovascular safety was evaluated in vitro and in vivo for cardiovascular effects to assess risk for dosing in clinical studies. The human ether-à-go-go-related gene (hERG) ion channel activity was found to be not significantly inhibited at concentrations up to 100 μM. Non-GLP hERG patch clamp assay (130227.TUC) did not reach half maximal response in current inhibition (12.9% inhibition at 100 μM). GLP hERG patch clamp assay (170111.DPW) did not reach half maximal response in hERG current inhibition (3.2% inhibition at 10 μM and 2.1% inhibition at 50 μM).

A dog telemetry study (8355826) 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 pharmacokinetic (PK)/pharmacodynamic (PD) sub-study of AG10-301 (48.2-fold margin).

Conclusions from the Non-clinical Development Programme

In conclusion, the totality of these non-clinical data indicates high levels of safety margins for acoramidis and low potential for adverse effects at anticipated therapeutic exposures. 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. The single PPND toxicity study in rats with adverse acoramidis-related effects at approximatively 80 times the projected human dose/AUC/concentration was taken into consideration.

The population studied in Study AG10-301, ATTR-CM patients, are not in their reproductive years. The cardiomyopathy population is usually > 60 years of age and male. Nevertheless, given the possibility of earlier diagnosis and progressively older age at which women may give birth, it may be possible that a woman with ATTR-CM may become pregnant. Therefore, reproductive and developmental toxicity is considered an important potential risk in the small subset of women of childbearing potential in the potential treatment population.

MODULE SIII Clinical Trial Exposure

Acoramidis has been studied in 14 completed or ongoing clinical studies including nine Phase I studies in healthy subjects, two Phase II studies in patients with symptomatic ATTR-CM (including the open-label extension study enrolling the population who have completed double-blind Study AG10-201) and three Phase III studies in patients with symptomatic ATTR-CM. In addition to these, an expanded access study in one subject with ATTR-CM has also been completed (Study AG10-999) (Table 3).

The pivotal Phase 3 study, AG10-301, the 30-month, randomised, double-blind, placebo-controlled study of acoramidis HCl 800 mg BID, served as the primary source of safety data for acoramidis in subjects with ATTR-CM.

Table 3: Acoramidis Summary of Completed and Ongoing Clinical Studies

Study Number	Study Design	Subjects	Regimen and dose[1]	Status
Phase I				
AG10-001	Randomised, placebo-controlled, single and multiple ascending dose study of the safety, tolerability, PK, PD	Healthy adult volunteers	Single dose: 50, 150, 300, 800 mg acoramidis (HCl) or placebo Multiple doses: 100, 300, 800 mg acoramidis (HCl) q12h or placebo for 12 days	Completed
AG10-003	Open label, single dose, 2 way crossover BE study of two acoramidis table formulations	Healthy adult volunteers	Single dose of acoramidis administered as 2 tablets of 200 mg acoramidis (HCl) or one tablet of 400 mg acoramidis (HCl)	Completed
AG10-004	Randomised open label two way crossover single dose study of safety, tolerability	Healthy adult Japanese and non-Japanese volunteers	Single dose of 400 mg or 800mg acoramidis (HCl) in period 1 followed by 7-day wash out period and crossover to the other dose in period 2	Completed
AG10-005	Randomised, placebo-controlled, single ascending dose study of 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	Completed
AG10-006	Open-label, 5-period study of PK of acoramidis modified release tablets	Healthy adult volunteers	Sigle doses of acoramidis 325, 625, and 1100 mg acoramidis (400, 702.2, and 1236 acoramidis HCl) in modified release tablets or 712 mg acoramidis (800 mg acoramidis HCl) in modified release plus 356 mg acoramidis (400 mg acoramidis HCl) in immediate release tablet in 5 Periods	Completed
AG10-007	Open label Absorption, Distribution, Metabolism, and Excretion (ADME) study of oral [14C] acoramidis	Healthy adult volunteers	A single dose of 800 mg acoramidis (HCl) (˜450 µCi) [^{14}C] acoramidis	Completed
AG10-008	Open label 2-part 2 period study of PK of acoramidis on PK of adefovir and oseltamivir carboxylate	Healthy adult volunteers	Part 1: 800 mg acoramidis (HCl) q12h plus 10 mg adefovir dipivoxil for 10 days Part 2: 800 mg acoramidis (HCl) q12h plus 75 mg oseltamivir phosphate for 12 days	Completed

Study Number	Study Design	Subjects	Regimen and dose[1]	Status
AG10-009	Single center, open-label, multiple-dose study to evaluate the PK of an acoramidis modified release tablet formulation	Healthy adult participants	Cohort 1/Regimen A: 1100 mg acoramidis MR tablet (2 × 550 mg tablets) QD on Days 1 to 7 in the fasted state Cohort 2/Regimen B: 1100 mg acoramidis MR tablet (12-20% HPMC K100LV; 2 × 550 mg tablets) QD on Days 1 to 7 in the fasted state	Ongoing
ALXN2060-HV-101	Randomised open label 2 period 2 sequence 2-way crossover food effect study of acoramidis	Healthy adult volunteers	A single dose of 800 mg acoramidis (HCl) fasted or fed	Completed
Phase II				
AG10-201	Randomised placebo-controlled dose ranging study of 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	Completed
AG10-202	Open label extension and safety monitoring study	Patients with symptomatic ATTR-CM who completed Study AG10-201	800 mg acoramidis (HCl) BID	Ongoing
Phase III				
AG10-301	Randomised double blind placebo-controlled study of efficacy and safety of acoramidis	Patients with symptomatic ATTR-CM	800 mg acoramidis (HCl) or placebo BID	Completed
AG10-304	Open label extension and safety monitoring study of acoramidis	Patient with symptomatic ATTR-CM who completed study AG10-301	800 mg acoramidis (HCl) BID	Ongoing
ALXN2060-TAC-302	Open label 2 part study of efficacy, safety, PK and PD of acoramidis	Japanese subjects with symptomatic ATTR-CM	800 mg acoramidis (HCl) or placebo BID	Ongoing
AG10-999	Expanded access	Symptomatic ATTR-CM	800 mg acoramidis HCl (4 x 200 mg tablets) BID	Completed

[1] Acoramidis 356 mg and 712 mg are equivalent to acoramidis HCl 400 mg and 800 mg, respectively.

Exposure

A total of 931 subjects have been enrolled in acoramidis clinical trials, of these, 792 subjects have been exposed to acoramidis (Table 4).

Table 4: Extent of Exposure to Acoramidis in the Clinical Programme

Treatment	Number of Subjects	
	Acoramidis	**Placebo**
AG10-001 single dose	24	8
AG10-001 multiple dose	18	6
AG10-003	24	0
AG10-004	19	0
AG10-005	18	9
AG10-006	14	0
AG10-007	6	0
AG10-008	32	0
AG10-009	28	0
AG10-201	32	17[1]
AG10-202 (open label ext AG10-201)	47[2]	0
AG10-301	421	211[3]
AG10-304 (open label ext AG10-301)	389[4]	0
AG10-999[5]	1	0
ALXN2060-HV-101[6]	18	0
ALXN2060-TAC-302[6]	25	0
TOTAL exposed to acoramidis (number of unique subjects)	**792[2a, 4a]**	**251**
TOTAL subjects (number of unique subjects, including placebo)	**931[7]**	

[1] All 17 Placebo subjects were enrolled in the open label Study AG10-202.
[2] Includes 30 subjects in the acoramidis arm and 17 subjects in placebo arm who completed Study AG10-201 and enrolled in the AG10-202 OLE study.
[2a] Subjects exposed to acoramidis in AG10-201 and AG10-202 are counted once in the total for subjects exposed to acoramidis.
[3] 95 Placebo subjects were enrolled in the open label extension Study AG10-304.
[4] Includes 294 subjects in the acoramidis arm and 95 subjects in placebo arm who completed Study AG10-301 and enrolled in the AG10-304 OLE study.
[4a] Subjects exposed to acoramidis in AG10-301 and AG10-304 are counted once in the total for subjects exposed to acoramidis.
[5] Expanded Access Use Protocol.
[6] Partner Alexion sponsored this study.
[7] Placebo subjects from studies AG10-201 and AG10-301 subsequently enrolled in open label extension studies AG10-202 and AG10-304 are only counted once in the total of unique subjects exposed.
Source: 2023 DSUR No. 6; data lock point 31AUG2023

Duration of Exposure

Extent of exposure in the Integrated Acoramidis Treatment Safety Analysis Set (Studies AG10-202 (ongoing), AG10-301 (completed) and AG10-304 (ongoing)) is summarised in Table 5.

Overall, the median duration of exposure to 800 mg acoramidis HCl BID was 2.47 years in the Integrated Acoramidis Treatment Safety Analysis Set (N = 563), with 343 (60.9%) participants receiving acoramidis for ≥ 2 years, and 25 (4.4%) receiving ≥ 4 years treatment.

Table 5: Summary of Extent of Acoramidis Treatment Exposure – Integrated Acoramidis Treatment 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.

Source: ISS Table 2.1.2.1; Data lock point: 27FEB2023

Demographics and Baseline Clinical Characteristics

Participant demographics and baseline characteristics of participants in AG10-202, AG10-304 and AG10-301 are summarised in Table 6. Overall, in the pivotal phase 3 AG10-301 study, the mean age at randomisation was 77.3 years (range, 50.3-91.0 years) and almost all (96.7%) of the 632 participants in the Safety Population were ≥ 65 years-of-age. Most participants were male (90.2%), White (87.8%), recently diagnosed with ATTR-CM (mean 1.2 years, range 0-10 years), of mostly wild-type (90.3%), and within New York Heart Association (NYHA) Class II (72.0%). Thirty participants (4.7%) were Black. At screening, overall most participants had eGFR ≥ 45 mL/min/1.73 m^2 (84.6% versus 15.4% of participants with eGFR < 45 mL/min/1.73 m^2).

In the Safety Population, baseline demographic characteristics were generally well balanced between the two treatment groups. There was a lower proportion of participants with NYHA Class II in the acoramidis treatment group than in the placebo group (69.6% versus 76.8%).

Table 6: Summary of Demographics and Baseline Characteristics – Integrated Acoramidis Treatment Safety Analysis Set

	AG10-202 Participants and AG10-301 Participants Treated with Acoramidis (N = 468)	AG10-304 Previously Treated with Placebo in AG10-301 (N = 95)	Overall (N = 563)
Age (years)			
n	468	95	563
Mean (SD)	77.17 (6.531)	79.44 (6.534)	77.55 (6.581)
Median (Q1, Q3)	78.00 (73.00, 82.00)	80.00 (75.00, 84.00)	78.00 (73.00, 83.00)
Min, Max	50.0, 90.0	59.0, 93.0	50.0, 93.0
Age Category (years)[a], n (%)			
< 65	14 (3.0%)	3 (3.2%)	17 (3.0%)
≥ 65 - < 78	214 (45.7%)	33 (34.7%)	247 (43.9%)
≥ 78	240 (51.3%)	59 (62.1%)	299 (53.1%)
Sex, n (%)			
Male	427 (91.2%)	92 (96.8%)	519 (92.2%)
Female	41 (8.8%)	3 (3.2%)	44 (7.8%)
Ethnicity, n (%)			
Hispanic or Latino	12 (2.6%)	2 (2.1%)	14 (2.5%)
Not Hispanic or Latino	443 (94.7%)	90 (94.7%)	533 (94.7%)
Not Reported	12 (2.6%)	3 (3.2%)	15 (2.7%)
Unknown	1 (0.2%)	0	1 (0.2%)
Race, n (%)			
Asian	11 (2.4%)	3 (3.2%)	14 (2.5%)
Black or African American	29 (6.2%)	0	29 (5.2%)
White	403 (86.1%)	88 (92.6%)	491 (87.2%)
Other	7 (1.5%)	0	7 (1.2%)
Multiple races	2 (0.4%)	0	2 (0.4%)
Not Reported	16 (3.4%)	4 (4.2%)	20 (3.6%)
BMI (kg/m^2)			
n	420	95	515
Mean (SD)	27.07 (3.793)	26.04 (3.723)	26.88 (3.798)
Median (Q1, Q3)	26.72 (24.46, 29.20)	25.42 (23.48, 28.60)	26.47 (24.24, 29.17)
Min, Max	18.1, 42.7	20.0, 37.8	18.1, 42.7

	AG10-202 Participants and AG10-301 Participants Treated with Acoramidis (N = 468)	AG10-304 Previously Treated with Placebo in AG10-301 (N = 95)	Overall (N = 563)
ATTR-CM Type			
ATTRm-CM	53 (11.3%)	3 (3.2%)	56 (9.9%)
ATTRwt-CM	415 (88.7%)	92 (96.8%)	507 (90.1%)
Baseline eGFR (mL/min/1.73m^2)[b]			
n	421	87	508
Mean (SD)	106.38 (39.860)	119.12 (36.324)	108.56 (39.536)
Median (Q1, Q3)	100.00 (82.10, 122.30)	111.10 (90.70, 140.50)	100.90 (83.65, 125.30)
Min, Max	37.0, 559.8	50.0, 224.4	37.0, 559.8
NYHA Class[c], n (%)			
I	51 (10.9%)	9 (9.5%)	60 (10.7%)
II	293 (62.6%)	54 (56.8%)	347 (61.6%)
III	77 (16.5%)	30 (31.6%)	107 (19.0%)
IV	0	1 (1.1%)	1 (0.2%)

Abbreviations: ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM; ATTRwt-CM = wildtype ATTR-CM; BMI = body mass index; eGFR = estimated glomerular filtration rate; NHYA = New York Heart Association; Q = Quartile; SD = standard deviation

[a] Age when being enrolled into the corresponding open-label extension studies, which was calculated as (open-label extension study informed consent date – birth date + 1) /365.25.

[b] eGFR was calculated using the Modification of Diet in Renal Disease equation.

[c] NYHA Class from 'NYHA Class Assessment' eCRF. NYHA Class Assessment is not available for Study AG10-202.

Source ISS Table 2.1.1.2.; Data lock point: 27FEB2023

MODULE SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Important exclusion criteria from the pivotal clinical study (AG10-301) are discussed in this section and presented below in Table 7.

Table 7: Exclusion Criteria in AG10-301 Pivotal Clinical Study

Exclusion Criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Severe Hepatic Compromise measured by: Abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) or total bilirubin > 3 × ULN.	The combination of heart failure from ATTRCM and chronic progressive hepatic impairment is a combination expected to lead to a very poor prognosis and therefore subjects with chronic progressive hepatic impairment were excluded. This approach is in line with the EMA protocol assistance final advice letter in January 2021 (EMEA/H/SA/4038/FU/1/2020/PA/III)	No	This approach is in line with the EMA protocol assistance final advice which stated The ATTR literature is almost devoid of mention of this sub-population presumably because of very low prevalence; the patient population are considered too ill to derive benefit from the medication. (EMEA/H/SA/4038/FU/1/2020/PA/III) Hepatic impairment is discussed in the SmPC Section 4.2 Posology and method of administration – Special populations; Section 4.4 Special warnings and precautions for use – Hepatic impairment; and Section 5.2 Pharmacokinetic properties – Special populations
Severe Renal compromise measured by: an eGFR by modification of diet for renal disease formula < 15 mL/min/1.73 m^2 at Screening.	Acoramidis does not have significant renal excretion and is eliminated primarily through metabolism (acylglucuronidation) (Study AG10-001). Patients with ATTR-CM and end stage renal function were excluded from pivotal clinical studies since they are unlikely to benefit from acoramidis therapy due to poor prognosis and limited predicted survival.	No	Acoramidis does not have significant renal excretion (< 10% is excreted in urine) and is eliminated primarily through metabolism; metabolised predominantly by glucuronidation (catalysed by multiple uridine 5'-diphosphate-glucuronosyltransferase [UGT] enzymes, with major contribution by UGT1A9, UGT2B7, and UGT1A1 and minor contribution by UGT1A3, UGT1A4, UGT1A6, UGT2B15, and UGT2B10), with acoramidis-AG being the predominant metabolite. Patients with severe renal impairment (estimated glomerular filtration rate between 15 and 30 mL/minute/1.73 m^2) were enrolled in the phase 3 study. Limited data are available in patients with severe renal impairment. Renal impairment is discussed in SmPC Section 4.2 Posology and method of administration – Special populations; and Section 5.2 Pharmacokinetic properties – Special populations.

Exclusion Criteria	Reason for Exclusion	Is it considered to be included as missing information?	Rationale
Has NT-proBNP levels ≥ 8500 pg/mL at screening	The patients with NT-proBNP levels ≥ 8500 pg/mL were excluded mainly to minimise interference with the assessment of the primary end point.	No	NT-proBNP levels are exploratory biomarkers with a high variability; and only patients who had NT-proBNP levels ≥ 8500 pg/mL at screening (after protocol AG10-301 Amendment 2.0) were excluded. It was not a protocol requirement to stop acoramidis treatment if the NT-proBNP levels raised ≥ 8500 pg/mL during treatment.
Patients with New York Heart Association (NYHA) Class IV symptoms due to ATTR-CM	Patients with NYHA Class IV due to ATTR-CM were excluded mainly to minimise interference with the assessment of the primary end point.	No	Patients with NYHA Class IV with ATTR-CM were unlikely to meet the eligibility criteria for 6-Minute Walk Test (6MWT) and unlikely to meaningfully contribute to the primary endpoint. Thus, this is not considered as missing information.
Females who are pregnant or breastfeeding	Effect in non-clinical studies (in pre-post-natal study in rat) were observed only at exposure considered sufficiently in excess of the maximum human exposure. Although this is considered as little relevance to clinical use, pregnant and breastfeeding subjects were excluded from clinical study	No	Studies in animals have shown developmental toxicity at doses which causes maternal toxicity. In the rat pre- and postnatal development study with acoramidis, decreased pup survival, reduced pup weights, and learning deficits were observed following maternal dose administration during pregnancy and lactation with acoramidis at 1000 mg/kg/day. Severe maternal toxicity including mortalities and weight loss during the period of organogenesis was also observed at this dose. In the pre-and postnatal development toxicity study in rats, the NOAEL was established at a dose of 350 mg/kg/day acoramidis HCl (AUC value approximately 21 times the AUC value observed in healthy volunteers at steady state of acoramidis HCl 80 mg q12h). ICH Guideline S5[R3] specifies there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD; above this threshold, concern is reduced. Effects that are limited to Maximum Recommended Human Dose (MRHD) occurrence at more than 25-fold the human exposure at the MRHD are usually of minor concern for the clinical use. Wide safety margins relative to human therapeutic exposures of acoramidis were identified in these studies. Pregnancy, lactation and fertility are discussed in the SmPC Section 4.6 Fertility, pregnancy and lactation; Section 5.3 Preclinical safety data; and in the Package leaflet: Information for the patient, No. 2.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions. Due to rarity of ATTR-CM the overall numbers of patients exposed to the product during the development was limited.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programme

Type of Special Population	Exposure
Pregnant Women	Not studied in the clinical programme. The protocol for each of the clinical studies excluded the participation of pregnant women. Across all studies if a woman became pregnant, she was to have stopped use of the study drug. One healthy volunteer became pregnant while on study AG10-001. The subject's treatment assignment was unblinded and she was counselled about her positive pregnancy and exposure to active study drug. The outcome of the pregnancy was unknown as the healthy volunteer was lost to follow up.
Breastfeeding women	Not studied in the clinical development programme. The protocol for each of the clinical studies excluded the participation of lactating women. There were no reports in the study programme concerning the use of acoramidis during lactation.
Patients with relevant comorbidities	
Patients with severe hepatic impairment	In study AG10-301, there were no participants that had an ALT or AST ≥ 3 x ULN + total bilirubin > 2 x ULN during routine and scheduled laboratory evaluation.
Patients with severe renal impairment	Acoramidis has not been studied in patients with severe renal compromise measured by: an eGFR by modification of diet for renal disease formula < 15 mL/min/1.73 m^2 at Screening. Renally impaired patients with an eGFR < 30 but ≥ 15 mL/min/1.73 m^2 were included in Study AG10-301. Subgroup analyses of adverse events (AE)s by eGFR group (≥ 30 versus < 30 mL/min/1.73 m^2 at Screening) are presented in Study AG10-301 Part B CSR, Section 12.5. 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). No safety signals of potential clinical concern were identified for acoramidis in the eGFR < 30 mL/min/1.73 m^2 subgroup.

Type of Special Population	Exposure
Immunocompromised patients	Not included in the clinical development programme
Patients with disease severity different from inclusion criteria in clinical trials	Subjects with most severe cases of heart failure = NYHA Class IV due to cardiomyopathy were excluded
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	transthyretin amyloidosis in adults (ATTR) wild-type or variant
Other	Not applicable

MODULE SV Post-authorisation Experience

No post-marketing data is available from EEA or other regions outside EEA for Acoramidis since this RMP is submitted within an initial marketing authorisation application.

SVI.1 Post-Authorisation Exposure

Not applicable.

MODULE SVI Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

There is no evidence that acoramidis has dependence potential. No drug abuse of acoramidis has been observed or is anticipated based on the pharmacology and receptor binding.

Acoramidis will be available as a prescription-only medication and dispensed as film coated tablets in blister packaging.

Based on the mechanism of action, availability and packaging, drug abuse and/or misuse is not anticipated with acoramidis.

MODULE SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Reproductive and developmental toxicity Kidney injury
Missing Information	None

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Acoramidis displayed a safety profile consistent with the patient population under study, with a similar rate, type, and severity of TEAEs. Acoramidis was generally well tolerated with no identified safety signals of potential clinical concern. There have been no adverse reactions identified for acoramidis.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important potential risk: Reproductive and developmental toxicity

In a single PPND toxicity study in rats, adverse acoramidis-related effects of proximal and spatial learning were noted in F_1 generation in rats with acoramidis at 1000 mg/kg/day. This corresponds to approximatively 80 times the projected human dose/AUC/concentration. The NOAEL in the PPND toxicity study in rats was established at the tested dose of acoramidis HCl 350 mg/kg/day (AUC values were approximatively 21-fold the human exposure at the clinical dose of acoramidis). There are no data on acoramidis in pregnant women as they were excluded from the clinical development programme.

Benefit-risk impact

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease. Study AG10-301 (ATTRibute-CM) demonstrated consistent treatment-related benefits of acoramidis across measures of mortality, morbidity, physical function, and QoL.

Patients diagnosed with ATTR-CM tend to be male, on average 60 years old or older.

Therefore, the chance of a woman of childbearing potential being exposed to acoramidis during pregnancy is negligible. As per ICH S5, in general, there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD; above this threshold, concern is reduced. Effects that are limited to occurrence at more than 25-fold the human exposure at the MRHD are usually of minor concern for the clinical use of the pharmaceutical.

Considering the observed adverse acoramidis-related effects come from a single PPND study in rats with exposures well above the ICH thresholds for clinical concern, the risk of injury to exposed women in pregnancy and their child is low.

Overall, the risk-benefit balance for acoramidis is positive considering the severity of the disease treated and the potential benefit for patients treated with acoramidis.

Important potential risk: Kidney injury

In Study AG10-301, the mean serum creatinine (and estimated GFR) at baseline was 110.0 µmol/L (eGFR: 60.9 mL/min/1.73 m^2) in the acoramidis group and 109.0 µmol/L (eGFR: 61.0 mL/min/1.73 m^2) in the placebo group. At Day 28, there was a change from baseline in the mean serum creatinine (eGFR) that was greater in the acoramidis group (observed values on Day 28 serum creatinine: 129.3 µmol/L, eGFR: 52.4 mL/min/1.73 m^2) compared with the placebo group (observed values on Day 28 serum creatinine: 110.6 µmol/L, eGFR: 60.0 mL/min/1.73 m^2). After Day 28, serum creatinine (eGFR) remained stable for these patients for the remainder of the study. There was a progressive rise in serum creatinine, and corresponding progressive decrease in eGFR, in the placebo group from baseline through Month 30. At Month 30, serum creatinine was 123.4 µmol/L (eGFR: 55.1 mL/min/1.73 m^2) and 117.2 µmol/L (eGFR: 57.2 mL/min/1.73 m^2) for acoramidis and placebo respectively. The observed increase in serum creatinine, and corresponding decrease in eGFR, observed in acoramidis treated patients was reversible upon interruption of therapy.

This change in eGFR and serum creatinine was non-progressive and reversible in those patients whose treatment was interrupted. Acoramidis has not been associated with kidney injury and these observations are consistent with a renal haemodynamic effect.

Benefit-risk impact

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease.

Worsening kidney function, both acute and chronic, is strongly associated with higher mortality and poor CV outcomes, especially heart failure hospitalisations (Hillege et al. 2006, Damman et al. 2009). In Study AG10-301, CV outcomes, including heart failure hospitalisations and mortality, and all-cause mortality were lower in the acoramidis group versus placebo group, suggesting that there was no apparent adverse effect of observed creatinine changes on these clinical outcomes.

The favourable profiles for both urine albumin-to-creatinine ratio (UACR) and urine albumin excretion (a marker of kidney injury) compared to placebo, lack of greater creatinine effects in participants with lower levels of baseline kidney function (i.e., eGFR < 60 mL/min/1.73 m^2), lack of evidence of worse kidney outcomes, and significantly improved CV outcomes and survival in participants treated with acoramidis (versus placebo) are, taken together, not consistent with kidney injury. These findings are consistent with a renal haemodynamic effect.

In the clinical context, intraglomerular hypertension provoking hyperfiltration is considered a risk factor for progression of chronic kidney disease (CKD). Lowering of intraglomerular pressure is the therapeutic goal of treatment of proteinuria, diabetic nephropathy, and other forms of chronic kidney disease (Anderson and Brenner 1986). Lowering of intraglomerular pressure is most often achieved with ACE inhibitors and ARBs, which are known to be renally protective, reducing the risk of progression to end-stage renal disease in patients with CKD (Gansevoort et al. 1993, Brenner et al. 2001, Jafar et al. 2001, Lewis et al. 2001, Holtkamp et al. 2011, Bakris et al. 2020). Several drug classes (e.g., sodium-glucose cotransporter 2 [SGLT2] inhibitors) are associated with both early, modest creatinine elevations and improved long-term cardiac and renal outcomes (Neuen et al. 2022).

Overall, the benefit-risk assessment for acoramidis is positive considering the severity of the disease treated and the potential benefit for patients treated with acoramidis.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

This is an initial marketing authorisation application.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential risks

Important potential risk: Reproductive and development toxicity

Potential mechanism

The adverse acoramidis-related effects on proximal and spatial learning of F_1 generation in rats are hypothesised to be secondary to maternal toxicity, although the precise mechanism has not been confirmed.

Evidence source and strength of evidence

The source of evidence is a single PPND toxicity study in rats (Study 8411736). The adverse acoramidis-related effects were noted in F_1 generation in rats at the highest dose of 1000 mg/kg/day (approximatively 80 times of the projected human dose/AUC/concentration). Severe maternal toxicity including mortalities and weight loss during the period of organogenesis was also observed at this dose. The NOAEL in the PPND toxicity study in rats was established at the tested dose of acoramidis HCl 350 mg/kg/day, (AUC values were approximatively 21-fold the human exposure at the clinical dose of acoramidis).

As per ICH S5, in general, there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD; above this threshold, concern is reduced. Effects that are limited to occurrence at more than 25-fold the human exposure at the MRHD are usually of minor concern for the clinical use of the pharmaceutical.

There are no data on acoramidis in pregnant women as they were excluded from the clinical development programme.

Considering the data are from a single PPND study in rats with exposures well above the ICH thresholds for clinical concern, and there are no data in pregnant women, evidence for this potential risk is weak.

Characterisation of the risk

The population studied in Study AG10-301, ATTR-CM patients, are not in their reproductive years. The cardiomyopathy population is usually > 60 years of age and male.

Considering the data are from a single PPND study with exposures well above the ICH thresholds for clinical concern, the risk of injury to exposed women in pregnancy and their child is low.

Risk factors and risk groups

Pregnant women and women of childbearing potential with the diagnosis of ATTR cardiomyopathy who are not using contraception are at risk.

Preventability

Acoramidis is not recommended during pregnancy and in women of childbearing potential not using contraception (SmPC, Section 4.6 Fertility, pregnancy, and lactation).

Impact on the risk-benefit balance

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease. Study AG10-301 (ATTRibute-CM) demonstrated consistent treatment-related benefits of acoramidis across measures of mortality, morbidity, physical function, and QoL.

Patients diagnosed with ATTR-CM tend to be male, on average 60 years old or older. Therefore, the chance of a woman of childbearing potential being exposed to acoramidis during pregnancy is negligible. Considering the observed adverse acoramidis-related effects come from a single PPND study in rats with exposures well above the ICH thresholds for concern, the risk of injury to exposed women in pregnancy and their child is low.

Overall, the risk-benefit balance for acoramidis is positive considering the severity of the disease treated and the potential benefit for patients treated with acoramidis.

Public health impact

Considering the negligible possibility of exposure of women of childbearing potential to acoramidis in this treatment population and routine risk minimisation measures to address this risk, the impact on public health is expected to be low.

Important potential risk: Kidney injury (MedDRA Acute kidney injury SMQ narrow terms)

Potential mechanism

In the acoramidis development programme, the pattern of the serum creatinine changes, favourable profiles for both UACR and urine albumin excretion (a marker of kidney injury) compared to placebo, and clinical outcomes favouring acoramidis over placebo are consistent with a renal hemodynamic effect of acoramidis and inconsistent with acute kidney injury (AKI).

This effect is the most likely mechanistic explanation for the creatinine/eGFR changes observed in the clinical trials based on the totality of data from the clinical and non-clinical development programmes.

In general, a relative dilation of the efferent versus afferent renal arterioles lowers intraglomerular pressure, which, in turn, lowers filtration (i.e., GFR). Hyperfiltration is a feature of CKD and reducing it has been shown to be renal-protective in the case of ARBs and SGLT-2 inhibitors. Such renal haemodynamic effects are typically associated with acute, modest, non-progressive increases in serum creatinine that reverse with removal of the factor(s) affecting renal haemodynamics. Such effects are not structural; rather, they are physiological, driven by the pharmacology of a number of drug classes that are believed to alter renal haemodynamics. Angiotensin converting enzyme inhibitors and ARBs, for example, inhibit the vasoconstrictive effect of angiotensin II on the efferent arteriole, resulting in an acute decline in the GFR by this mechanism. Treatment with these drugs results in an initial reduction in eGFR that stabilises after several months. In the long-term, ACE inhibitor and ARBs have been shown to improve kidney outcomes such as time to development of end-stage kidney disease or doubling of serum creatinine (Gansevoort et al. 1993, Brenner et al. 2001, Jafar et al. 2001, Holtkamp et al. 2011)). Similar acute, but reversible, effects on eGFR are observed with the SGLT-2 inhibitor drug class. While the precise physiologic basis of the creatinine/eGFR changes with these drugs has not been established for SGLT-2 inhibitors and the pattern of renal laboratory findings is not consistent with various transporters, there is a presumed role of acute haemodynamic changes based on the totality of the data.

Evidence source and strength of evidence

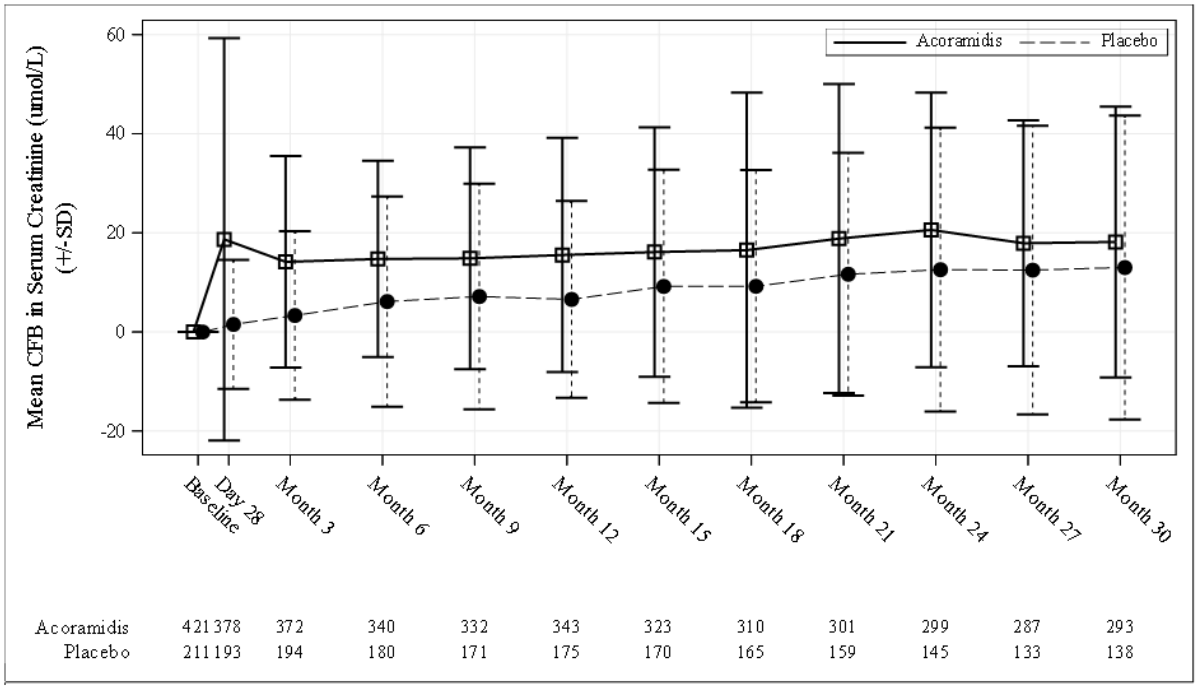
The pattern of renal laboratory observations seen in the acoramidis development programme, the pattern of the serum creatinine changes, favourable profiles for both UACR and urine albumin excretion (a marker of kidney injury) compared to placebo, clinical outcomes favouring acoramidis over placebo, and lack of association with renal AEs are consistent with a renal haemodynamic effect of acoramidis and inconsistent with AKI.

Characterisation of the risk

Laboratory data (serum creatinine, UACR, and urine albumin excretion) and eGFR were evaluated in Study AG10-301. The stable creatinine pattern seen in this study after 28 days of treatment is inconsistent with what would be expected with continued long-term treatment with a drug that caused kidney injury. Ongoing treatment with such a drug would be expected to result in a progressive increase in serum creatinine relative to placebo.

In Study AG10-301, the mean serum creatinine (and estimated GFR) at baseline was 110.0 µmol/L (eGFR: 60.9 mL/min/1.73 m^2) in the acoramidis group and 109.0 µmol/L (eGFR: 61.0 mL/min/1.73 m^2) in the placebo group. At Day 28, there was a change from baseline in the mean serum creatinine (eGFR) that was greater in the acoramidis group (observed values on Day 28 serum creatinine: 129.3 µmol/L, eGFR: 52.4 mL/min/1.73 m^2) compared with the placebo group (observed values on Day 28 serum creatinine: 110.6 µmol/L, eGFR: 60.0 mL/min/1.73 m^2). After Day 28, serum creatinine (eGFR) remained stable for these patients for the remainder of the study. There was a progressive rise in serum creatinine, and corresponding progressive decrease in eGFR, in the placebo group from baseline through Month 30. At Month 30, serum creatinine was 123.4 µmol/L (eGFR: 55.1 mL/min/1.73 m^2) and 117.2 µmol/L (eGFR: 57.2 mL/min/1.73 m^2) for acoramidis and placebo respectively. The observed increase in serum creatinine, and corresponding decrease in eGFR, observed in acoramidis treated patients was reversible following interruption of therapy.

Figure 1: Change from Baseline in Serum Creatinine Over Time (Study AG10-301)



Abbreviations: CFB = change from baseline; SD = standard deviation
Source: Post-hoc Figure 14.6.1.5

Data from Phase 2 studies AG10-201 and AG10-202, and the Phase 3 study AG10-301 show that the mean creatinine rose promptly (ie, by the first postbaseline visit at Day 14 or Day 28, respectively) and remained stable during the course of treatment. Following an interruption of treatment with acoramidis, the observed increase in creatinine following initiation of treatment was reversed. The lack of a progressive rise in the mean serum creatinine over time and the reversibility of creatinine upon treatment interruption are consistent with a non-adverse mechanism for the creatinine (eg, a potential renal haemodynamic effect) and inconsistent with kidney injury.

The favourable profiles for both UACR and urine albumin excretion (a marker of kidney injury) are seen in the acoramidis group compared to placebo. Albuminuria is an established marker of kidney damage/injury and severity of albuminuria predicts progression of chronic kidney disease (Levey et al. 2005). In the AG10-301 study, treatment with acoramidis was not associated with evidence of kidney injury as assessed by albuminuria.

Worsening kidney function, both acute and chronic, is strongly associated with higher mortality and poor CV outcomes, especially heart failure hospitalisations (Hillege et al. 2006, Damman et al. 2009). In this study, CV outcomes, including CV-related hospitalisations (26.7% vs. 42.6%), LS mean change from baseline in the 6MWT (-64.65 vs. -104.29), as well as CV-mortality (14.9% vs. 21.3%) and overall mortality (19.3% vs. 25.7%) were better in the acoramidis group versus the placebo group, suggesting that there was no apparent adverse effects of the observed creatinine changes on these clinical outcomes.

These findings of better CV outcomes in the acoramidis group are inconsistent with drug-induced kidney injury because kidney injury is strongly associated with worse cardiovascular clinical outcomes.

The adverse events reported in Study AG10-301 with PTs matching events in Medical Dictionary for Regulatory Activities (MedDRA) Acute renal failure Standardised MedDRA Query (SMQ) (narrow terms) have been evaluated. A summary of data for these events is provided in Table 9 below. The most frequently reported events (> 5%) were PTs of acute kidney injury with frequency of 12.4% on acoramidis and 10.4% on placebo, and renal impairment with frequency of 8.8% on acoramidis and 8.1% on placebo. The most frequently reported SAE was the PT of acute kidney injury (5% on acoramidis and 3.8% on placebo). There were no events with fatal outcome reported. Adverse events considered drug-related by the investigator on acoramidis were PTs of renal impairment (0.7%) and on placebo was the PT of renal failure (0.5%). The majority of the events were of mild or moderate intensity across both treatment groups. The events reported with severe intensity were the PTs of acute kidney injury (2.6% on acoramidis and 2.4% on placebo), renal impairment (1.2% on acoramidis and 0 on placebo), and prerenal failure (0.2% on acoramidis and 0 on placebo). Although, there is a small imbalance in the frequency of reported events with PT acute kidney injury between the acoramidis and placebo groups, the overall characteristics of these events are similar between the treatment groups: none were considered drug related by the investigator, the frequencies for the severity of the events were similar between the treatment groups, none of the events were with fatal outcome, the majority of the events resolved, were resolving or resolved with sequalae and the majority did not require dose modification. Two participants with events of acute kidney injury in the acoramidis group and 0 on placebo discontinued treatment.

Overall, these findings together do not suggest an overall increased risk of kidney injury associated with acoramidis treatment, and are consistent with a renal haemodynamic effect.

Table 9: Summary of TEAEs with PTs in MedDRA Acute Renal Failure SMQ (Narrow Terms) Reported in Study AG10-301

MedDRA Acute renal failure SMQ (Narrow terms) TEAEs – Preferred terms (PT)	**Acoramidis (N = 421) n (%) E**	**Placebo (N = 211) n (%) E**
PT Acute kidney injury[1]	**52 (12.4%) 64**	**22 (10.4%) 30**
Serious[2]	21 (5.0%) 21	8 (3.8%) 8
Drug related[3]	0	0
Severity[4]		
Mild	16 (3.8%)	8 (3.8%)
Moderate	25 (5.9%)	9 (4.3%)
Severe	11 (2.6%)	5 (2.4%)
Fatal outcome[5]	0	0
PT Nephropathy toxic[1]	**1 (0.2%) 1**	**2 (0.9%) 2**
Serious[2]	1 (0.2%) 1	2 (0.9%) 2
Drug related[3]	0	0
Severity[4]		
Mild	0	0
Moderate	1 (0.2%)	2 (0.9%)
Severe	0	0
Fatal outcome[5]	0	0
PT Prerenal failure[1]	**1 (0.2%) 1**	**0**
Serious[2]	1 (0.2%) 1	0
Drug related[3]	0	0
Severity[4]		
Mild	0	0
Moderate	0	0
Severe	1 (0.2%)	0
Fatal outcome[5]	0	0
PT Renal failure[1]	**7 (1.7%) 7**	**3 (1.4%) 3**
Serious[2]	0	0
Drug related[3]	0	1 (0.5%) 1
Severity[4]		
Mild	1 (0.2%)	1 (0.5%)
Moderate	6 (1.4%)	2 (0.9%)
Severe	0	0
Fatal outcome[5]	0	0

MedDRA Acute renal failure SMQ (Narrow terms) TEAEs – Preferred terms (PT)	Acoramidis (N = 421) n (%) E	Placebo (N = 211) n (%) E
PT Renal impairment[1]	**37 (8.8%) 42**	**17 (8.1%) 17**
Serious[2]	3 (0.7%) 3	0
Drug related[3]	2 (0.5%) 2	0
Severity[4]		
Mild	10 (2.4%)	7 (3.3%)
Moderate	22 (5.2%)	10 (4.7%)
Severe	5 (1.2%)	0
Fatal outcome[5]	0	0

[1] Source: AG10-301 CSR, Table 14.3.1.2.
[2] Source: AG10-301 CSR, Table 14.3.1.9.
[3] Source: AG10-301 CSR, Table 14.3.1.5.
[4] Source: AG10-301 CSR, Table 14.3.1.3.
[5] Source: AG10-301 CSR, Table 14.3.1.17.

Lastly, the data from studies in nonclinical species (listed below) showed no evidence of glomerular or tubular injury (e.g., tubular regeneration or necrosis) observed on histopathological examination.

In a 26-week toxicity study in rats (Study 20141689) at doses of 50 mg/kg/day, 300 mg/kg/day, and 600 mg/kg/day, there were no noteworthy renal findings. The safety margin was wide (19-fold based on C_{max} and 43-fold based on AUC) compared to human exposure at 2000 mg acoramidis HCl.

In a 39-week toxicity study in dogs (Study 20141692) at doses of 50 mg/kg/day, 112 mg/kg/day, and 250 mg/kg/day, there were no noteworthy renal findings. The safety margin was wide (14-fold based on C_{max} and 16-fold based on AUC) compared to human exposure at 2000 mg acoramidis HCl.

Risk factors and risk groups

No risk factors or groups were identified including from analysis in the subgroup of patients with eGFR < 30 mL/min/1.73 m^2 at screening.

Preventability

Renal laboratory changes were reversible in those patients whose treatment was interrupted.

Impact on the risk-benefit balance

ATTR amyloidosis is a rare, multisystem, progressive, debilitating, and ultimately fatal disease

Worsening kidney function, both acute and chronic, is strongly associated with higher mortality and poor CV outcomes, especially heart failure hospitalisations (Hillege et al. 2006, Damman et al. 2009). In Study AG10-301, CV outcomes, including heart failure hospitalisations and mortality, and all-cause mortality were lower in the acoramidis group versus placebo group, suggesting that there was no apparent adverse effect of observed creatinine changes on these clinical outcomes.

The favourable profiles for both UACR and urine albumin excretion (a marker of kidney injury) compared to placebo, lack of greater creatinine effects in participants with lower levels of baseline kidney function (i.e., eGFR < 60 mL/min/1.73 m^2), lack of evidence of worse kidney outcomes, and significantly improved CV outcomes and survival in participants treated with acoramidis (versus placebo) are, taken together, not consistent with kidney injury. These findings are consistent with a renal haemodynamic effect.

In the clinical context, intraglomerular hypertension provoking hyperfiltration is considered a risk factor for progression of chronic kidney diseases. Lowering of intraglomerular pressure is the therapeutic goal of treatment of proteinuria, diabetic nephropathy, and other forms of chronic kidney disease (Anderson and Brenner 1986). Lowering of intraglomerular pressure is most often achieved with ACE inhibitors and ARBs, which are known to be renally protective, reducing the risk of progression to end-stage renal disease in patients with CKD (Gansevoort et al. 1993, Brenner et al. 2001, Jafar et al. 2001, Lewis et al. 2001, Holtkamp et al. 2011, Bakris et al. 2020). Several drug classes (e.g., SGLT-2 inhibitors) are associated with early, modest creatinine elevations but improved long-term cardiac and renal outcomes (Neuen et al. 2022).

Overall, the benefit-risk assessment for acoramidis is positive considering the severity of the disease treated and the potential benefit for patients treated with acoramidis.

Public health impact

Considering that findings are not consistent with kidney injury and routine risk minimisation measures address this risk, the impact on public health is expected to be low.

SVII.3.2 Presentation of the Missing Information

Not applicable.

MODULE SVIII Summary of the Safety Concerns

Table 10: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Reproductive and developmental toxicity Kidney injury
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities include (but are not limited to):

- Collection, collation, assessment, and reporting of spontaneous reports;
- Periodic literature surveillance; and
- Signal detection activities.

Routine pharmacovigilance practice includes comprehensive post-marketing surveillance assessment of spontaneously reported events with expedited reporting in compliance with worldwide regulatory requirements, and submission of Periodic Safety Update Reports (PSURs) in accordance with applicable regulatory requirements.

Periodic safety evaluation of cumulative data will also be conducted to evaluate safety signals. If a safety signal is identified, further assessment and characterisation of the safety signal will be conducted, including evaluation of individual case reports and aggregate data analysis.

New safety information will be communicated to the regulatory authorities worldwide, in accordance with local regulations. Additional activities may include product label revisions and updates with new safety information, discussion with regulatory authorities, and informational letters to the treating physicians.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires

None proposed

Other forms of routine pharmacovigilance activities

None proposed

III.2 Additional Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 11: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Important Potential Risks	
Reproductive and developmental toxicity	Routine risk communications: Relevant information is provided in SmPC Section 4.6 Fertility, pregnancy, and lactation; Section 5.3 Preclinical safety data; and in Package leaflet: Information for patients, No. 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Kidney injury	Routine risk communications 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. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Acoramidis

This is a summary of the risk management plan (RMP) for BEYONTTRA. The RMP details important risks of BEYONTTRA, how these risks can be minimised, and how more information will be obtained about BEYONTTRA's risks and uncertainties (missing information).

BEYONTTRA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how acoramidis should be used.

This summary of the RMP for BEYONTTRA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BEYONTTRA's RMP.

VI.1 The medicine and what it is used for

BEYONTTRA is indicated for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). It contains acoramidis as the active substance and is taken orally. BEYONTTRA is a white, oval film-coated tablets approximately 15 mm with the BridgeBio company logo followed by "ACOR" in black ink on one side. Each film-coated tablet contains 356 mg of acoramidis equivalent to 400 mg of acoramidis hydrochloride.

Further information about the evaluation of BEYONTTRA's benefits can be found in BEYONTTRA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

VI.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important potential risks of BEYONTTRA, together with measures to minimise such risks, are outlined below.

Routine risk minimisation measures for acoramidis include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

VI.2A List of important risks and missing information

Important risks of acoramidis are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of acoramidis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risks	None
Important Potential Risks	Reproductive and developmental toxicity Kidney injury
Missing Information	None

VI.2.B Summary of important risks

Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	The source of evidence is a single PPND toxicity study in rats (Study 8411736). The adverse acoramidis-related effects were noted in F_1 generation in rats at the highest dose of 1000 mg/kg/day (approximatively 80 times of the projected human dose/AUC/concentration). Severe maternal toxicity including mortalities and weight loss during the period of organogenesis was also observed at this dose. The NOAEL in the PPND toxicity study in rats were established at the tested dose of acoramidis HCl 350 mg/kg/day (AUC values were approximatively 21-fold the human exposure at the clinical dose of acoramidis. As per ICH S5, in general, there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the MRHD; above this threshold, concern is reduced. Effects that are limited to occurrence at more than 25-fold the human exposure at the MRHD are usually of minor concern for the clinical use of the pharmaceutical. There are no data on acoramidis in pregnant women as they were excluded from the clinical development programme. Considering the data are from a single PPND study in rats with exposures well above the ICH thresholds for clinical concern, and there are no data in pregnant women, evidence for this potential risk is weak.
Risk factors and risk groups	Pregnant women and women of childbearing potential with the diagnosis of ATTR cardiomyopathy who are not using contraception are at risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 Fertility, pregnancy, and lactation • SmPC Section 5.3 Preclinical safety data • SmPC Package leaflet: Information for patients, No. 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risk: Kidney injury	
Evidence for linking the risk to the medicine	The pattern of renal laboratory observations seen in the acoramidis development programme, the pattern of the serum creatinine changes, favourable profiles for both UACR and urine albumin excretion (a marker of kidney injury) compared to placebo, clinical outcomes favouring acoramidis over placebo, and lack of association with renal AEs are consistent with a renal haemodynamic effect of acoramidis and inconsistent with AKI.
Risk factors and risk groups	No risk factors or groups were identified including from analysis in the subgroup of patients with eGFR < 30 mL/min/1.73 m^2 at screening.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use – Renal haemodynamic parameters • SmPC Section 5.1. Pharmacodynamic properties • SmPC Package leaflet: Information for patients, No. 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

VI.2.C Post-authorisation development plan

VI.2.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of acoramidis.

VI.2.C.2 Other studies in post-authorisation development plan

There are no studies required for Acoramidis.

PART VII: ANNEXES

TABLE OF CONTENTS

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable.

Annex 7 – Other supporting data (including referenced material)

Agbor-Etang BB, Okafor HE, Farber-Eger EH, Wells QS. Low prevalence of clinically apparent cardiac amyloidosis among carriers of transthyretin V122I variant in a large electronic medical record. Am J Med. 2021;134(2):e98-e100.

Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G, et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. Eur J Heart Fail. 2022;24(12):2342-51.

Almeida MR, Alves IL, Terazaki H, Ando Y, Saraiva MJ. Comparative studies of two transthyretin variants with protective effects on familial amyloidotic polyneuropathy: TTR R104H and TTR T119M. Biochem Biophys Res Commun. 2000;270(3):1024-8.

Anderson S, Brenner BM. The role of lntraglomerular pressure in the initiation and progression of renal disease. J Hypertens Suppl. 1986;4(5):S236-S8.

Arno S, Cowger J. The genetics of cardiac amyloidosis. Heart Fail Rev. 2022;27(5):1485-92.

Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219-29.

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.

Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. JAMA Cardiol. 2016;1(8):880-9.

Castaño A, Maurer MS. 22 - Cardiac Amyloidosis. In: Felker GM, Mann DL, editors. Heart failure: a companion to Braunwald's heart disease (fourth edition). Philadelphia: Elsevier; 2019. p. 301-10.e3.

Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). Eur J Heart Fail. 2009;11(9):847-54.

Dispenzieri A, Coelho T, Conceicao I, Waddington-Cruz M, Wixner J, Kristen AV, et al. Clinical and genetic profile of patients enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS): 14-year update. Orphanet J Rare Dis. 2022;17(1):236.

Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, et al. Canadian cardiovascular society/Canadian heart failure society joint position statement on the evaluation and management of patients With cardiac amyloidosis. Can J Cardiol. 2020;36(3):322-34.

Fosbol EL, Rorth R, Leicht BP, Schou M, Maurer MS, Kristensen SL, et al. Association of carpal tunnel syndrome with amyloidosis, heart failure, and adverse cardiovascular outcomes. J Am Coll Cardiol. 2019;74(1):15-23.

Gansevoort RT, de Zeeuw D, de Jong PE. Dissociation between the course of the hemodynamic and antiproteinuric effects of angiotensin I converting enzyme inhibition. Kidney Int. 1993;44(3):579-84.

Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2021a;23(6):895-905.

Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. 2021b;23(4):512-26.

Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404-12.

Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015;36(38):2585-94.

Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671-8.

Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int. 2011;80(3):282-7.

ICH M3[R2]. *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. FDA-2008-D-0470*. 2009.

ICH S2[R1]. *Genotoxicity testing and data interpretation for pharmaceuticals intended for human use (FDA-2008-D-0178)*. 2012.

ICH S5[R3]. *Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals (FDA-2017-D-5138)*. 2020.

Ioannou A, Fontana M, Gillmore JD. Patisiran for the treatment of transthyretin-mediated amyloidosis with cardiomyopathy. Heart Int. 2023;17(1):27-35.

Ioannou A, Patel RK, Razvi Y, Porcari A, Sinagra G, Venneri L, et al. Impact of earlier diagnosis in cardiac ATTR amyloidosis over the course of 20 years. Circulation. 2022;146(22):1657-70.

Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135(2):73-87.

Kitaoka H, Izumi C, Izumiya Y, Inomata T, Ueda M, Kubo T, et al. JCS 2020 Guideline on Diagnosis and Treatment of Cardiac Amyloidosis. Circ J. 2020;84(9):1610-71.

Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary are for the patient with cardiac amyloidosis: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol. 2023;81(11):1076-126.

Lauppe R, Liseth Hansen J, Fornwall A, Johansson K, Rozenbaum MH, Strand AM, et al. Prevalence, characteristics, and mortality of patients with transthyretin amyloid cardiomyopathy in the Nordic countries. ESC Heart Fail. 2022;9(4):2528-37.

Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67(6):2089-100.

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-60.

Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075.

Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007-16.

Merlo M, Pagura L, Porcari A, Cameli M, Vergaro G, Musumeci B, et al. Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from Phase 2 of the AC-TIVE study, an Italian nationwide survey. Eur J Heart Fail. 2022;24(8):1377-86.

Neuen BL, Tighiouart H, Heerspink HJL, Vonesh E, Chaudhari J, Miao S, et al. Acute treatment effects on GFR in Randomized clinical trials of kidney disease progression. J Am Soc Nephrol. 2022;33(2):291-303.

Obi CA, Mostertz WC, Griffin JM, Judge DP. ATTR epidemiology, genetics, and prognostic factors. Methodist Debakey Cardiovasc J. 2022;18(2):17-26.

Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-91.

Soares ML, Coelho T, Sousa A, Batalov S, Conceicao I, Sales-Luis ML, et al. Susceptibility and modifier genes in Portuguese transthyretin V30M amyloid polyneuropathy: complexity in a single-gene disease. Hum Mol Genet. 2005;14(4):543-53.

Vyndaqel-EPAR. Assessment report: Vyndaqel, International non-proprietary name: tafamidis, Procedure No. EMEA/H/C/002294/X/0049/G. 2019.

Vyndaqel-FDA-CDER. Assessment Report: Vyndaqel, International non-proprietary name: tafamidis, Application No. 211996 and 212161. 2019.

Westin O, Fosbol E, Gustafsson F. Refining the role of carpal tunnel syndrome in cardiac amyloidosis. Eur J Heart Fail. 2020;22(3):516-8.

Yilmaz A, Bauersachs J, Bengel F, Buchel R, Kindermann I, Klingel K, et al. Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021;110(4):479-506.