▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

BEYONTTRA 356 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains acoramidis hydrochloride equivalent to 356 mg acoramidis.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated by a physician knowledgeable in the management of patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

Posology

The recommended dose of acoramidis is 712 mg (two tablets, 356 mg) orally, twice daily, corresponding to a total daily dose of 1 424 mg.

There are no efficacy data in patients with New York Heart Association (NYHA) Class IV (see section 5.1).

Missed dose

No double dose should be taken to make up for missed individual doses. Dosing should resume at the next scheduled time.

Special populations

Elderly

No dose adjustment is required in elderly patients (≥ 65 years, see section 5.2).

Renal impairment

Based on low renal clearance of acoramidis, no dose adjustment is required (see section 5.2). Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited (see sections 4.4 and 5.2) and there are no data for patients on dialysis. Hence acoramidis should be used with caution in this population.

Hepatic impairment

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

Paediatric population

There is no relevant use of acoramidis in the paediatric population for the indication of "the treatment of wild-type or variant transthyretin amyloidosis with cardiomyopathy".

Method of administration

Oral use.

The film-coated tablets should be swallowed whole. BEYONTTRA can be taken with water, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic impairment

Acoramidis has not been studied in patients with hepatic impairment and therefore is not recommended for use in this population (see sections 4.2 and 5.2).

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited (see sections 4.2 and 5.2) and there are no data for patients on dialysis. Hence acoramidis should be used with caution in this population.

Renal haemodynamic parameters

Patients treated with acoramidis experienced an initial decrease in estimated glomerular filtration rate (eGFR) in the first month of treatment and a corresponding increase in measured serum creatinine (see section 5.1).
This change in eGFR and serum creatinine was non-progressive, reversible in those patients whose treatment was interrupted, and not associated with kidney injury, consistent with a renal haemodynamic effect.

Information about excipients

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of acoramidis on other medicinal products

Transporter systems

Based on a clinical study in healthy adult volunteers, inhibition of organic anion transporter (OAT)-1 and -3 is not expected to result in clinically relevant drug-drug interactions with OAT-1 and OAT-3 substrates (e.g., non-steroidal anti-inflammatory medicines, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine).

Based on an *in vitro* study, no drug-drug interaction with co-administered breast cancer resistance protein (BCRP) substrates is anticipated at clinically relevant concentrations.

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

Effect of other medicinal products on acoramidis

Diuretics

Based on population pharmacokinetic (PK) analysis, concomitant diuretic use in patients does not affect steady-state plasma acoramidis concentrations.

Breast Cancer Resistance Protein inhibitors

Acoramidis is a substrate for BCRP. Based on an *in vitro* study, a clinically relevant interaction with BCRP inhibitors is not expected.

Gastric acid reducing agents

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

Effect on laboratory test

Acoramidis may decrease serum concentrations of free thyroxine without an accompanying change in thyroid stimulating hormone (TSH). No corresponding clinical findings consistent with thyroid dysfunction have been observed.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are no data on the use of acoramidis in pregnant women.

Studies in animals have shown developmental toxicity at a dose which also caused maternal toxicity (see section 5.3). Acoramidis is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether acoramidis or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded (see section 5.3). Acoramidis should not be used during breast-feeding.

Fertility

No human data on fertility is available. Impairment of fertility has not been observed in non-clinical studies in supratherapeutic exposures.

4.7 Effects on ability to drive and use machines

BEYONTTRA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Based on the clinical study, the most frequently reported adverse reactions were diarrhoea (11.6%) and gout (11.2%).

Tabulated list of adverse reactions

The safety data reflect exposure of 421 participants with ATTR-CM to acoramidis 712 mg (as two tablets of 356 mg) administered orally twice daily in a pivotal Phase 3 randomised, double-blind, placebo-controlled study of 30 months fixed treatment duration in patients diagnosed with ATTR-CM.

Adverse reactions are listed below by MedDRA System Organ Class (SOC) and frequency categories using the standard convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), and Uncommon (≥ 1/1 000 to < 1/100). Adverse reactions listed in the table below are from cumulative clinical data in ATTR-CM participants.

Table 1: List of adverse reactions

System Organ Class	**Very common**
Gastrointestinal disorders	Diarrhoea
Metabolism and nutrition disorders	Gout

Description of selected adverse reactions

The majority of events of diarrhoea and gout were non-serious and resolved.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
Belgium
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
www.fagg.be
Afdeling Vigilantie:
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg-afmps.be

Luxembourg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Netherlands
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

4.9 Overdose

There is no clinical experience with overdose.

In case of suspected overdose, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, Other cardiac preparations. ATC code: C01EB25.

Mechanism of action

Transthyretin amyloid cardiomyopathy is initiated by the dissociation of the transthyretin (TTR) tetramer into its constituent monomers. These misfold and aggregate as oligomeric amyloid precursors that deposit in the heart where they assemble into amyloid fibrils.

Acoramidis is a specific stabiliser of TTR. 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 ATTR-CM.

Pharmacodynamic effects

Near-complete transthyretin stabilisation was observed with acoramidis in wild-type and in all amyloidogenic variant genotypes tested, including the most prevalent genotypes V30M (p.V50M), T60A (p.T80A), and V122I (p.V142I). In the ATTRibute-CM study, in patients (wild-type and variant ATTR) treated with acoramidis (712 mg twice daily), near-complete (≥ 90%) TTR stabilisation was observed at the first post-dose initiation assessment (Day 28) and sustained through Month 30. For all post-baseline measurements (from Day 28 through Month 30), the TTR level was higher in the acoramidis group compared with placebo (at Month 30, mean change from baseline 9.1 mg/dL with acoramidis versus 1.3 mg/dL with placebo).

In ATTRibute-CM, the increase in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at Month 30 favoured acoramidis and was about half the increase seen with placebo. A lower increase in troponin I was also observed with acoramidis versus placebo.

In ATTRibute-CM, 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 in the acoramidis group 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 in the event of an interruption of therapy.

Cardiac electrophysiology

The maximum dose of acoramidis, 1 780 mg, studied as a single dose in healthy adult volunteers did not have a clinically relevant effect on cardiac conduction or repolarisation (no concentration-QTc effect was observed). These observations indicate a low risk of pro-arrhythmia.

Clinical efficacy

ATTRibute-CM was a multicentre, international, randomised, double-blind, placebo-controlled clinical study conducted in 632 participants with wild-type or variant (hereditary or de novo) ATTR-CM and heart failure NYHA Class I-III, with current or prior symptoms of heart failure. Participants were randomised in a 2:1 ratio to receive acoramidis 712 mg (n = 421), or matching placebo (n = 211) twice daily for 30 months. Treatment assignment was stratified by whether participants had variant ATTR-CM (ATTRv-CM) or wild-type ATTR-CM (ATTRwt-CM) and baseline disease severity, i.e., NT-proBNP level and renal function as defined by eGFR. Patients with eGFR < 15 mL/min/1.73 m^2 were excluded from participation in the study.

Table 2: Demographics and baseline characteristics (mITT population[1])

Characteristic	**Acoramidis N = 409**	**Placebo N = 202**
Age — years		
Mean (standard deviation)	77.3 (6.5)	77.0 (6.7)
Sex — number (%)		
Male	374 (91.4)	181 (89.6)
Female	35 (8.6)	21 (10.4)
TTR genotype[2] — number (%)		
ATTRv	39 (9.5)	20 (9.9)
ATTRwt	370 (90.5)	182 (90.1)
NYHA class — number (%)		
NYHA class I	51 (12.5)	17 (8.4)
NYHA class II	288 (70.4)	156 (77.2)
NYHA class III	70 (17.1)	29 (14.4)
eGFR[2] (mL/min/1.73 m^2) – number (%)		
eGFR ≥ 45	344 (84.1)	173 (85.6)
eGFR < 45	65 (15.9)	29 (14.4)
NT-proBNP[2] (pg/mL) – number (%)		
≤ 3 000	268 (65.5)	133 (65.8)
> 3 000	141 (34.5)	69 (34.2)

Characteristic	Acoramidis N = 409	Placebo N = 202
ATTR NAC stage[3] — number (%)		
I	241 (58.9)	120 (59.4)
II	130 (31.8)	66 (32.7)
III	38 (9.3)	16 (7.9)
History of permanent pacemaker – number (%)	77 (18.8)	38 (18.8)
History of atrial fibrillation – number (%)	236 (57.7)	117 (57.9)

Abbreviations: ATTRv = variant transthyretin amyloid, ATTRwt = wild-type transthyretin amyloid, NAC = National Amyloidosis Centre (London UK), NYHA = New York Heart Association, eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, TTR = transthyretin

1 mITT = modified intent to treat (baseline eGFR ≥ 30 mL/min/1.73 m^2).

2 Stratification factors.

3 NAC Stage I (NT-proBNP ≤ 3 000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2), Stage II (NT-proBNP ≤ 3 000 pg/mL and eGFR < 45 mL/min/1.73 m^2 or NT-proBNP > 3 000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2), Stage III (NT-proBNP > 3 000 pg/mL and eGFR < 45 mL/min/1.73 m^2).

Participants were permitted to initiate open label tafamidis if prescribed as a concomitant medicinal product after 12 months in the study. A total of 107 participants received tafamidis, 61 (14.9%) in the acoramidis arm and 46 (22.8%) in the placebo arm.

The primary objective of the study was to establish superiority of acoramidis versus placebo on a hierarchical endpoint that included all-cause mortality (ACM) and cumulative frequency of cardiovascular-related hospitalisation (CVH). Secondary objectives included assessment of ACM, CVH, 6-minute walk distance, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (a measure of quality of life), serum TTR level and NT-proBNP. The main efficacy analyses were conducted in the 611 participants in the modified intent to treat (mITT) population without any adjustment for the introduction of open label tafamidis.

Efficacy analysis

The efficacy analysis applied the stratified Finkelstein-Schoenfeld (F-S) test hierarchically to ACM and CVH over the 30-month study. The method compared each participant to every other participant within each stratum in a pair-wise manner. In this hierarchical approach, participants in each pair are first compared on ACM, and then on CVH only if the comparison on ACM resulted in a tie. The result of this analysis was statistically significant (Table 3).

All-cause mortality was reported in 19.3% and 25.7% of participants in the acoramidis and placebo groups, respectively. The majority (79%) of deaths were cardiovascular (CV)-related with acoramidis demonstrating a 30% relative risk reduction in CV-related mortality compared with placebo. CV-related mortality was reported in 14.9% and 21.3% of participants in the acoramidis and placebo groups, respectively; hazard ratio: 0.709 (95% CI: 0.476, 1.054, p = 0.0889, Cox proportional hazards model).

A Cox regression analysis indicated a 35.5% decrease in the risk of the composite of ACM or first CV hospitalisation (hazard ratio: 0.645 [95% CI: 0.500, 0.832; p = 0.0008]). Separation in the Kaplan-Meier curves was observed at Month 3 and steadily diverged through Month 30 (Figure 1).

The efficacy results on ACM and CVH demonstrated in the mITT population were also observed in the ITT population (all randomised subjects irrespective of baseline eGFR).

Table 3: Efficacy results on Finkelstein-Schoenfeld analysis, all-cause mortality and cardiovascular-related hospitalisation at Month 30 in ATTRibute-CM (mITT population)

Parameter	Acoramidis N = 409	Placebo N = 202
Combination of ACM and cumulative frequency of CVH		
Win ratio (95% CI)	1.464 (1.067, 2.009)	
F-S[1] p-value	p = 0.0182	
Number (%) of participants alive at Month 30[2]	330 (80.7%)	150 (74.3%)
Number (%) of participants with CVH	109 (26.7%)	86 (42.6%)
Number of total CVH events	182	170
Frequency of CVH per year per participant (mean)[3]	0.29	0.55
Relative risk ratio[4]	0.496	
p-value	p < 0.0001	

Abbreviations: F-S = Finkelstein-Schoenfeld; ACM = all-cause mortality; CVH = cardiovascular hospitalisation; mITT = modified intent-to-treat; CI = confidence interval

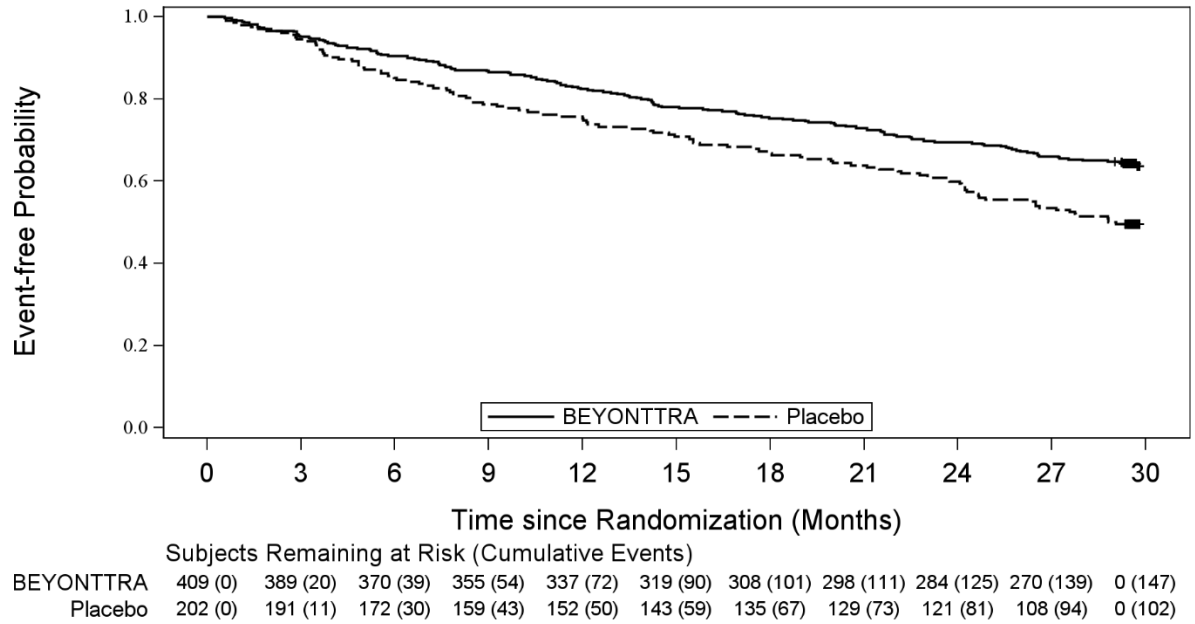
1 The F-S method compares every participant pair within each stratum in a hierarchical fashion, starting with ACM. If pairs are tied on ACM, they are then assessed on CVH.

2 Heart transplantation and cardiac mechanical assist device implantation are considered indicators of approaching end stage. As such, these events are treated in the analysis as equivalent to death. Therefore, such participants are not included in the count of "Number of participants alive at Month 30" even if such participants are alive based on 30-month vital status follow-up assessment. Vital status at Month 30 was known for all participants.

3 CVH per year for each participant is calculated as (participant's total number of observed CVH) / (duration of follow-up in years) and include events of clinical interest (EOCI). EOCI is defined as medical visits (e.g., emergency department/ward, urgent care clinic, day clinic) of < 24 hours for intravenous diuretic therapy for management of decompensated heart failure.

4 From negative binomial regression model.

Figure 1: Time to all-cause mortality or first cardiovascular-related hospitalisation



6-Minute Walk Distance (6MWD) and KCCQ

The treatment effect of acoramidis on functional capacity and health status was assessed by the 6MWD and the KCCQ Overall Summary score (KCCQ-OS); composed of the physical limitation, symptom, social limitation and quality of life domains), respectively (Table 4). A treatment effect favouring acoramidis was first observed for 6MWD and KCCQ-OS at Month 18 and Month 3, respectively, and was sustained through Month 30.

Table 4: 6MWD and KCCQ-OS scores

	Baseline Mean (SD)		**Change from Baseline to Month 30, LS Mean (SE)**		**Treatment Difference from Placebo LS Mean (96% CI)**	
Endpoints*	**Acoramidis N = 409**	**Placebo N = 202**	**Acoramidis N = 409**	**Placebo N = 202**		**p-value**
6MWD (metres)	362.78 (103.50)	351.51 (93.83)	-64.65 (5.51)	-104.29 (7.77)	39.64 (20.18, 59.10)	< 0.0001
KCCQ-OS	71.73 (19.37)	70.48 (20.65)	-11.48 (1.18)	-21.42 (1.65)	9.94 (5.79, 14.10)	< 0.0001

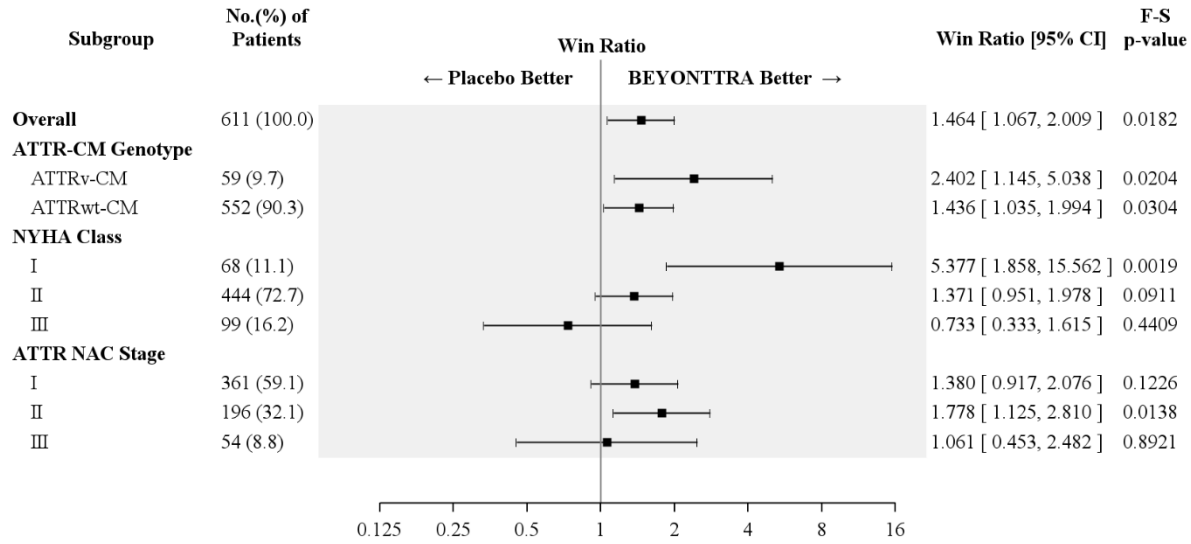
Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score, LS = least squares, SD = standard deviation, SE = standard error

* Higher values indicate better health status.

Subgroup analysis

Results from the F-S test applied to ACM and CVH (complemented by the win ratio) consistently favoured acoramidis versus placebo across the stratification parameter (wild type or variant), NYHA class and ATTR National Amyloidosis Centre (NAC) stage subgroups (Figure 2).

Figure 2: Hierarchical combination of all-cause mortality and CV-related hospitalisation, Finkelstein-Schoenfeld and win ratio results overall and by subgroup (mITT population)[1]



Abbreviations: ACM = all-cause mortality; ATTRwt-CM = wild-type ATTR-CM; ATTRv-CM = variant ATTR-CM; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; NAC = National Amyloidosis Centre (London, UK); NYHA = New York Heart Association; NAC Stage I (NT-proBNP ≤ 3 000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2), Stage II (NT-proBNP ≤ 3 000 pg/mL and eGFR < 45 mL/min/1.73 m^2 or NT-proBNP > 3 000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2), Stage III (NT-proBNP > 3 000 pg/mL and eGFR < 45 mL/min/1.73 m^2)

[1] The win ratio is the number of pairs with acoramidis treated-participant "wins" divided by number of pairs with placebo-treated participant "wins."

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with BEYONTTRA in all subsets of the paediatric population in ATTR-CM (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The increase in exposure parameters (area under the concentration-time curve [AUC] and maximum concentration [C_{max}]) was less than dose-proportional over single (up to 1 780 mg) or multiple (up to 712 mg) twice daily dosing.

Following oral administration, acoramidis is rapidly absorbed and peak plasma concentration of unchanged acoramidis is usually achieved within 1 hour. Increases in plasma concentration were observed for acoramidis doses from 44.5 mg once daily to 712 mg once daily. Plasma exposures appeared to saturate at acoramidis doses over 712 mg to 1 068 mg. A steady state is achieved by 10 days of dosing with 712 mg twice daily, and repeated dosing results in minor (approximately 1.3- to 1.6-fold) accumulation of acoramidis.

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

The overall extent of absorption of acoramidis is not influenced by food intake.

Distribution

The apparent steady state volume of distribution of 712 mg acoramidis dosed twice daily is 654 litres. *In vitro* binding of acoramidis to human plasma proteins is 96.4%. Acoramidis primarily binds to TTR.

Biotransformation

The metabolism of acoramidis was characterised following the administration of a single oral dose of [^{14}C]-acoramidis to healthy adult volunteers. Acoramidis is metabolised predominantly by glucuronidation, with acoramidis-β-D-glucuronide (acoramidis-AG) being the predominant metabolite (7.6% of total circulating radioactivity). Acoramidis-AG is approximately 3-fold less pharmacologically active than acoramidis, has a low potential for covalent binding, and does not meaningfully contribute to pharmacological activity.

Elimination and excretion

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

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

Special populations

No clinically significant differences in the pharmacokinetics of acoramidis were observed based on age (18.0-89.3 years), race/ethnicity (including Japanese and non-Japanese), sex, or renal impairment (eGFR 25.4-157 mL/min/1.73 m^2).

Based on population PK modelling, steady-state acoramidis AUC was 37% higher for healthy subjects than for the patient population. Also, relative to White subjects, steady-state AUC was 23% higher for Black subjects and 38% higher for non-White, non-Black subjects. These effects are within the range of inter-individual variability (CV = 38%). The model also predicted lack of clinically significant differences in the pharmacokinetics of acoramidis due to body weight, within the body weights range of 50.9 to 133 kg.

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

Acoramidis has not been studied in patients with hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, developmental and reproductive toxicology (fertility and embryo-foetal development).

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 1 000 mg/kg/day. Severe maternal toxicity including mortalities and weight loss during the period of organogenesis was also observed at this dose. The no-observed-adverse-effect-level (NOAEL) in pre- and postnatal development toxicity study in rats were established at the tested dose of 350 mg/kg/day acoramidis, (AUC values were approximatively 21-fold the human exposure at the clinical dose of acoramidis).

Placental transfer and milk excretion studies in animals were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460)
Croscarmellose sodium (E 468)
Colloidal hydrated silica (E 551)
Magnesium stearate (E 470b)

Film-coat

Macrogol poly(vinyl alcohol) grafted copolymer (E 1209)
Talc (E 553b)
Titanium dioxide (E 171)
Glyceryl monocaprylocaprate Type I (E 471)
Poly(vinyl alcohol) (E 1203)

Printing ink

Iron oxide black (E 172)
Propylene glycol (E 1520)
Hypromellose 2910 (E 464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs – Thermoformed dual-cavity blisters of PVC/PCTFE with aluminium foil lidding

Pack sizes: 120 tablets in 6 blister strips, each with 10 cavities (2 tablets per cavity)

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BridgeBio Europe B.V.
Weerdestein 97
Amsterdam, 1083 GG
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1906/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

02/2025

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu.