swissmedic

Date: 10 February 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

BEYONTTRA

International non-proprietary name:	acoramidis as acoramidis hydrochloride
Pharmaceutical form:	film-coated tablet
Dosage strength(s):	356 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Bayer (Schweiz) AG
Marketing authorisation no.:	70089
Decision and decision date:	approved on 18 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATTR-CM	Transthyretin amyloid cardiomyopathy
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for acoramidis as acoramidis hydrochloride in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 11 February 2025.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose is 712 mg (two tablets, 356 mg) orally, twice daily, corresponding to a total daily dose of 1,424 mg (4 tablets).

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	14 February 2025
Formal objection	13 March 2025
Response to formal objection	25 March 2025
Formal control completed	8 April 2025

Preliminary decision	26 June 2025
Response to preliminary decision	21 August 2025
Labelling corrections and/or other aspects	28 October 2025
Response to labelling corrections and/or other aspects	19 November 2025
Final decision	18 December 2025
Decision	approval

Based on Art. 13 TPA Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, EMA. This SwissPAR relates to the assessment report Beyonttra, procedure No. EMEA/H/C/006333/0000, 12 December 2024, issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones).

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA (see section 2.3 Regulatory history (milestones)).

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. (see section 2.3 Regulatory history (milestones).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for BEYONTTRA was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

BEYONTTRA

Composition

Active substances

Acoramidisum ut Acoramidisi hydrochloridum

Excipients

Tablet core: Cellulosum microcristallinum (E 460), Carmellosum natricum conexum (E 468), Silica colloidalis hydrica (E 551), Magnesii stearas (E 470b)
Film-coat: Copolymerum macrogolo et alcoholi poly(vinylico) constatum (E 1209), Talcum (E 553b), Titanii dioxidum (E 171), Glyceroli monocaprylocapras, Typ I (E 471), Poly(alcohol vinylicus) (E 1203)
Printing ink: Ferrum oxydatum nigrum (E 172), Propylenglycolum (E 1520), Hypromellosum (E 464)

Pharmaceutical form and active substance quantity per unit

Film-coated tablets of 356 mg Acoramidis as Acoramidis hydrochloride.
White, oval film-coated tablets approximately 15 mm × 7.5 mm with the printing “BEYONTTRA” in black ink on one side.

Indications/Uses

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

Dosage/Administration

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

Recommended dosage

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 Clinical Efficacy).

Missed dose

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

Method of administration

Oral use.

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

Special dosage instructions

Patients with hepatic impairment

Acoramidis has not been studied in patients with hepatic impairment and therefore is not recommended for use in this population (see sections “Warnings and precautions” and “Pharmacokinetics”).

Patients with renal impairment

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

Elderly

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

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”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Hepatic impairment

Acoramidis has not been studied in patients with hepatic impairment and therefore is not recommended for use in this population (see sections “Dosage/Administration” and “Pharmacokinetics”).

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited (see sections “Dosage/Administration” and “Pharmacokinetics”) 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 “Properties/Effects”).

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.

Sodium

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

Interactions

Effect of other substances on the pharmacokinetics of 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 of acoramidis on the pharmacokinetics of other substances

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 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.

Pregnancy, 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 ”Preclinical Data”). Acoramidis is not recommended during pregnancy and in women of childbearing potential not using an effective contraception method.

Breast-feeding

It is unknown whether acoramidis or its metabolites are excreted in human milk. A risk to the breastfed child cannot be excluded (see section “Preclinical Data”). 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.

Effects on ability to drive and use machines

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

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%).

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 that occurred during clinical studies are summarized below by MedDRA System Organ Class and frequency. The following frequency categories are used: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥1/10,000, <1/1000), Very rare (<1/10,000) and Frequency not known.

Metabolism and nutrition disorders

Very common: Gout (11,2%)

Gastrointestinal disorders

Very common: Diarrhoe (11,6%)

Description of selected adverse reactions

The majority of events of diarrhoea and gout were non-serious and resolved.Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no clinical experience with overdose.
In case of suspected overdose, treatment should be symptomatic and supportive.

Properties/Effects

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.

Pharmacodynamics

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 m2) in the acoramidis group and 109.0 µmol/L (eGFR: 61.0 mL/min/1.73 m2) 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 m2) compared with the placebo group (observed values on Day 28 serum creatinine: 110.6 µmol/L, eGFR: 60.0 mL/min/1.73 m2). 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 m2) and 117.2 µmol/L (eGFR: 57.2 mL/min/1.73 m2) 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 m2 were excluded from participation in the study.

Table 1: 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)
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 2).

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 2: 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

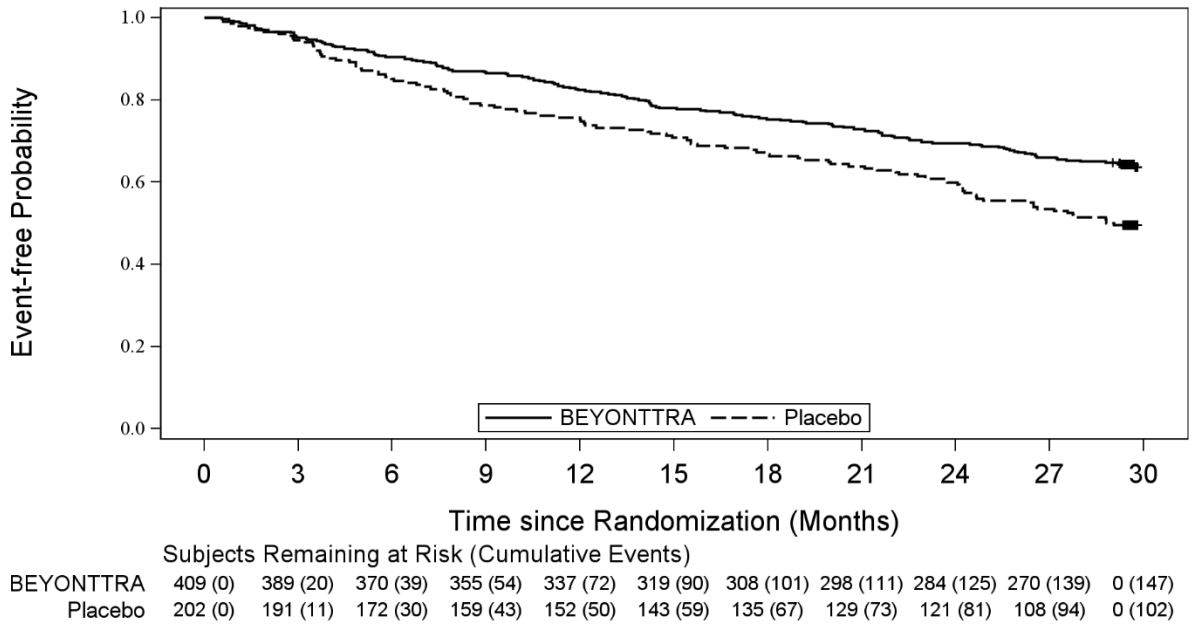
1 The F-S method compares every participant pair within each stratum in a hierarchical fashion, starting with ACM. If pairs are tied on ACM, they are then assessed on CVH.

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 3). 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 3: 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)**	**p-value**
Endpoints*	**Acoramidis N = 409**	**Placebo N = 202**	**Acoramidis N = 409**	**Placebo N = 202**		
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

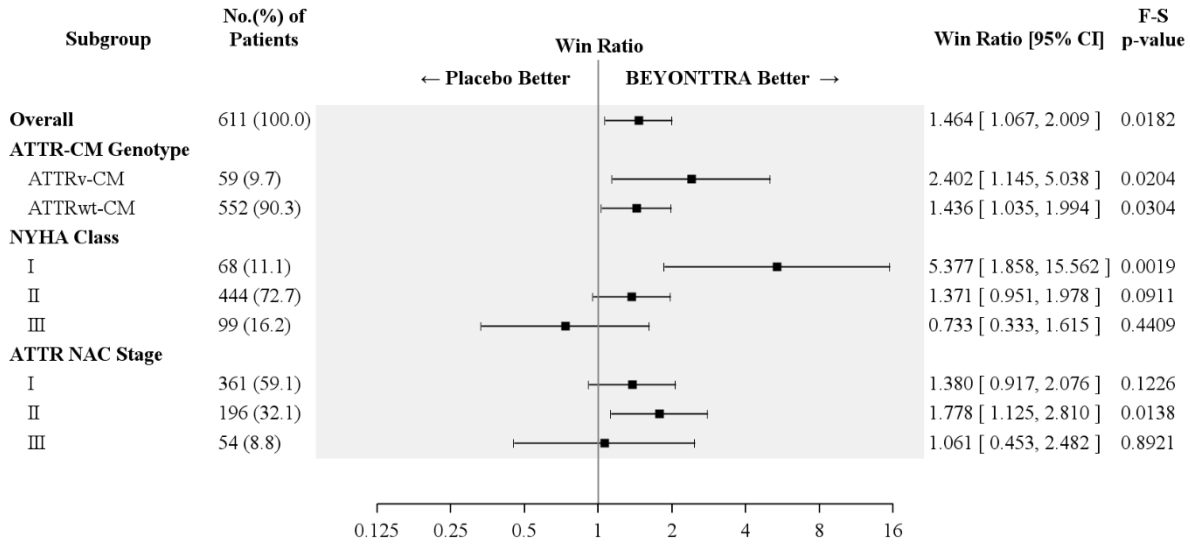
Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score, LS = least squares, SD = standard deviation, SE = standard error

* 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

Swissmedic has waived the obligation to submit the results of studies with BEYONTTRA in all subsets of the paediatric population in ATTR CM (see section “Dosage/Administration – paediatric population”).

Pharmacokinetics

Absorption

The increase in exposure parameters (area under the concentration-time curve [AUC] and maximum concentration [Cmax]) 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.

Metabolism

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

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 [14C]-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%.

Kinetics in specific patient groups

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 m2).

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.

Preclinical 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Instructions for handling

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

Authorisation number

70089 (Swissmedic)

Packs

BEYONTTRA 356 mg: packs of 120 tablets [B]

Marketing authorisation holder

Bayer (Schweiz) AG, Zürich

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