Rationale and Design of ACO-SWITCH – A Phase 4 Study Evaluating Serum Transthyretin Levels in Patients With ATTR-CM who Switched From Tafamidis to Acoramidis

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INTRODUCTION

- Acoramidis is a transthyretin (TTR) stabiliser approved for the treatment of wild-type and variant transthyretin amyloid cardiomyopathy (ATTR-CM) in the United States, European Union, Japan, the United Kingdom, and Switzerland, based on positive results versus placebo in the Phase 3 ATTRibute-CM study (NCT03860935), including a reduced composite of all-cause mortality and cardiovascular hospitalisations.[1–6]
- Acoramidis is one of two TTR stabilisers approved for the treatment of ATTR-CM in Europe, the other being tafamidis.[2,7]
- Serum TTR (sTTR) is the starting point in the pathophysiology of amyloid development and deposition and has potential as a marker of ATTR-CM disease activity and response to TTR stabiliser treatment.[8–10]
- Tafamidis stabilises TTR via binding at thyroxine (T4) binding sites and has shown clinical benefits in patients with ATTR-CM.[7,11]
- Acoramidis achieves near-complete (>90%) stabilisation through strong, enthalpically driven interactions with TTR, forming hydrogen bonds at the T4 binding site that mimic the stabilising effects of the disease-protective T119M variant of TTR.[12,13]
- The uniquely high binding affinity and TTR stabilisation of acoramidis[14] may result in higher sTTR levels, which has been associated with improved survival,[10] than with tafamidis.
- ACO-SWITCH (NCT07298044) will evaluate the change in sTTR levels, biomarkers, and other parameters, in acoramidis-treated adult participants with ATTR-CM who were previously treated with tafamidis.

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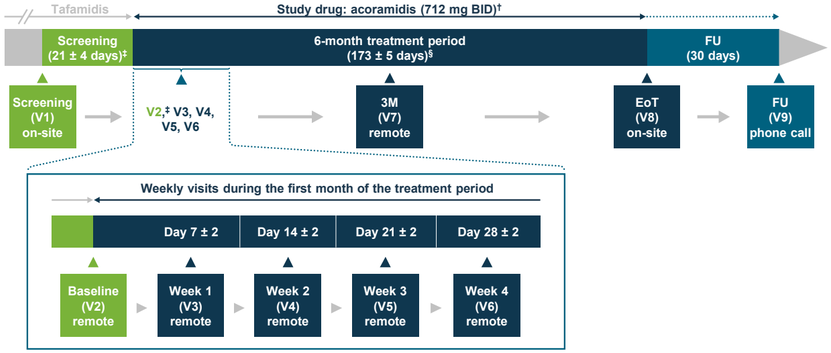
METHODS

Study design

- ACO-SWITCH is an ongoing, prospective, open-label, single-arm, multicentre, Phase 4, low-intervention study planned to evaluate the course of sTTR with acoramidis in 50 participants who have used tafamidis for ≥3 months prior to the start of the study (**Figure 1**).
- The study will be conducted in approximately 20 study sites in several European countries, including Austria, Germany, and Italy.

Figure 1. ACO-SWITCH study design



†Acoramidis (712 mg BID) may be continued after the treatment period if prescribed by the investigator. ‡Adherence to tafamidis is monitored using a diary during the 21-day screening period. To join the study, participants must not have missed intake of tafamidis treatment on more than 6 days per month. At Visit 2, participants with tafamidis intake on <80% of days during screening will be withdrawn from the study. §During the treatment period, compliance with the study drug will be monitored at Visits 3–8.
On-site visits take place at the study site. Remote visits are conducted by a home care nurse at the participant's home.
BID, twice daily; EoT, end of treatment; FU, follow-up; M, months; V, visit.

Study participants

- Key participant inclusion and exclusion criteria are summarised in **Table 1**.

Table 1. Key participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults (18–90 years of age at the date of signing the ICF) • Diagnosis of variant or wild-type ATTR-CM within 24 months prior to Visit 1 • Adherence to current tafamidis treatment that has been used for at least the previous 3 months prior to Visit 1 • New York Heart Association class ≤II • eGFR ≥30 mL/min/1.73 m^2 • N-terminal pro-B-type natriuretic peptide >300 pg/mL and ≤7000 pg/mL • Stable disease for ≥3 months	• ATTR-CM-related hospitalisation within 3 months prior to Visit 1 • Heart failure due to ischaemic heart disease • Myocardial infarction, cardiovascular surgery, or unstable angina within the past 90 days prior to Visit 1 • Confirmed diagnosis of light-chain amyloidosis • Dialysis or severe renal impairment • Known or suspected liver disorder • Current patisiran, vutrisiran, or inotersen; marketed drugs lacking a labelled indication for ATTR-CM (e.g. diflunisal, doxycycline), unproven therapies, or investigational drugs for ATTR-CM • Recent treatment with sodium-glucose cotransporter 2 inhibitors or diuretics

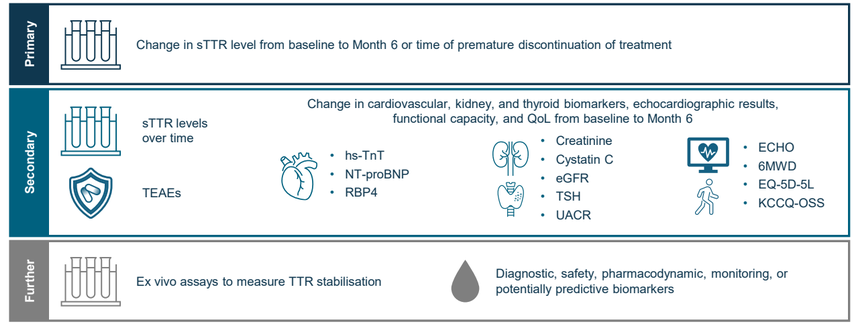
ATTR-CM, transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; ICF, informed consent form.

- Participants will be switched from tafamidis to acoramidis after a 21-day run-in period.
- To minimise the burden on participants, study visits will be conducted at the participants' homes by a study nurse, whenever possible.

Study objectives

- The primary objective is to evaluate the change in sTTR level associated with acoramidis treatment in participants with ATTR-CM who switched from tafamidis, from baseline to Month 6 or time of premature discontinuation of treatment (**Figure 2**).
- Secondary objectives include: sTTR levels at baseline, Weeks 1, 2, 3, 4, and Month 3; biomarkers and functional capacity; laboratory parameters related to kidney and thyroid function; quality of life; and safety.

Figure 2. Study endpoints



6MWD, 6-minute walk distance; ECHO, echocardiography; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol-5-Dimension-5-Level; hs-TnT, high-sensitivity troponin T; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life; RBP4, retinol-binding protein 4; sTTR, serum transthyretin; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone; TTR, transthyretin; UACR, urinary albumin–creatinine ratio.

Analysis

- Mean change in sTTR will be evaluated using a one-sided paired Wilcoxon signed-rank test.
- Statistical analyses for endpoints other than the primary endpoint will be exploratory and descriptive.
- Efficacy analyses will be conducted for the full analysis set (all enrolled participants); safety analyses will be conducted for all enrolled participants who received at least one dose of study treatment.

CONCLUSIONS

- ACO-SWITCH is a prospective study in adult participants with variant or wild-type ATTR-CM who switched from tafamidis treatment (at study entry) to acoramidis for up to 6 months.
- The study aims to determine whether acoramidis induces an additional increase in sTTR concentration after treatment with tafamidis.
- Results from this study may provide evidence to support clinical decision-making in patients with ATTR-CM.