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Newcastle University

Health Technology Briefing
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Acoramidis for symptomatic transthyretin amyloid cardiomyopathy

Company/Developer	BridgeBio Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 24010	NICE TSID: Not available	UKPS ID: 669985

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Acoramidis is in clinical development for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-CM is an underdiagnosed, progressively debilitating, rare disease associated with high mortality. ATTR-CM occurs when a protein called transthyretin (TTR) becomes unstable and aggregates, forming amyloids, and deposits primarily in the heart, as well as other organs, known as transthyretin amyloidosis. This damages the structure and function of the organs and causes serious disease which can be fatal. It causes the thickening and stiffening of the heart tissues. Symptoms include shortness of breath, palpitations and abnormal heart rhythms, ankle swelling, fatigue, fainting and chest pain. Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care. However, heart and/or liver transplantation may be an option for some patients if appropriate, although rare.

Acoramidis acts as a stabiliser of TTR. Acoramidis mimics the action of a naturally occurring protective mutation of the TTR gene. This mutation has been shown to prevent or minimise the formation of TTR amyloids in individuals who carry disease-causing mutations in the TTR gene. After being taken by mouth it attaches to TTR in the blood, which prevents the abnormal protein from breaking up and forming amyloids. This is expected to slow down the progression of the disease. If licensed, acoramidis would offer a novel treatment option for ATTR-CM patients.

Proposed Indication

For the treatment of wild-type or hereditary symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) in adult patients aged 18 – 90 years.[1]

Technology

Description

Acoramidis is an investigational, orally-administered small molecule designed to potently stabilise tetrameric transthyretin (TTR). Acoramidis was designed to mimic a naturally occurring variant of the TTR gene (T119M) that is considered a 'rescue mutation' because it has been shown to prevent or minimise ATTR in individuals carrying pathogenic, or disease-causing, mutations in the TTR gene.[2] After being taken by mouth it attaches to TTR in the blood, which prevents the abnormal protein from breaking up and forming amyloids. This is expected to slow down the progression of the disease.[3]

Acoramidis is in clinical development for the treatment of symptomatic ATTR-CM. In the phase III clinical trial (ATTRibute-CM, NCT03860935), 800mg acoramidis hydrochloride (HCl) will be administered twice daily as an oral tablet.[1]

Key Innovation

Acoramidis is a potent, highly selective TTR stabiliser. Compared with other known stabilisers, acoramidis is unique in its capacity to form hydrogen bonds with the same serine residues at position 117 that stabilise the T119M variant. This, coupled with the current observations of its ability to increase serum TTR in ATTR-CM patients, has potentially important clinical implications. Acoramidis could prove to be an important option amongst new, disease-modifying treatments, together transforming ATTR from an inevitably progressive, fatal disorder into a treatable chronic disease.[4] The oral bioavailability of acoramidis, combined with additional desirable drug-like features, makes it a very promising candidate to treat ATTR-CM.[5]

If licensed, acoramidis would offer a treatment option for ATTR-CM patients.

Regulatory & Development Status

Acoramidis does not currently have Marketing Authorisation in the UK/EU for any indication.

Acoramidis has the following regulatory designations/awards:[3]

- Orphan drug designation in the EU in 2018 for the treatment of ATTR amyloidosis

Patient Group

Disease Area and Clinical Need

Transthyretin amyloidosis (ATTR) is a rare, life-threatening disease resulting from aggregation and deposition of TTR amyloid fibrils in various tissues. There are two predominant phenotypic presentations of the disease: hereditary ATTR with polyneuropathy, which primarily affects the peripheral nerves, and ATTR-CM, which primarily affects the heart and includes both wild-type and hereditary forms.[6] ATTR is caused by destabilisation of TTR due to pathogenic mutations or aging.[4] Hereditary ATTR-CM is characterised by a single amino acid substitution caused by a point mutation in the TTR gene, and wild-type ATTR-CM is a non-familial form of the disease that predominantly presents in elderly male patients.[7]

Amyloid fibrils of misfolded TTR protein accumulate in the heart leading to cardiomyopathy and symptoms of heart failure including dyspnoea, fatigue, orthostatic hypotension and syncope. Additionally, infiltration of the conduction system can lead to bundle branch block, atrioventricular block, sinoatrial disease, and atrial fibrillation.[6] However, cardiac symptoms are often proceeded by musculoskeletal manifestation such as carpal tunnel syndrome. ATTR-CM is usually misdiagnosed, particularly early in its course owing to non-specific symptoms and multi system involvement.[7]

Data from the National Amyloidosis Centre in the UK reports that about 1,000 new cases of amyloidosis (including all different types) are diagnosed each year.[8] Since the diagnosis of ATTR-CM is challenging and often missed, the true disease prevalence remains unknown.[9] In the UK, there are thought to be around 600 people with wildtype ATTR-CM and 200 people with hereditary ATTR-CM. The number of new diagnoses made each year, particularly for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of non-invasive diagnostic tests.[10] In England (2021-22), there were 3,147 finished consultant episodes (FCE) and 2,540 admissions for organ-limited amyloidosis (ICD-10 code E85.4). This resulted in 7,184 FCE bed days and 1,981 day cases.[11] The median survival of untreated ATTR-CM with V122I mutation (the most common mutation in hereditary ATTR-CM) is 2.5 years for hereditary ATTR-CM and 3.6 years for wild-type ATTR-CM.[7]

Recommended Treatment Options

Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care such as diuretics.[10] Liver transplantation, which prevents the formation of additional amyloid deposits by removing the main source of abnormal TTR production, or heart transplantation, are options for some people with ATTR-CM and a specific genetic mutation. However, this mutation is uncommon in England, and transplantation can only take place early in the course of the disease, so it is very rarely used in England.[10] There are currently no pharmacological therapies recommended by NICE for the treatment of ATTR-CM.[12]

Clinical Trial Information

Trial	NCT04988386; **EudraCT** 2020-005643-22; An Open-Label Extension and Safety Monitoring Study of Acoramidis (AG10) in Participants With Symptomatic Transthyretin Amyloid Cardiomyopathy Who Completed the Phase 3 ATTRibute-CM Trial (AG10-301) **Phase III** – enrolling by invitation **Location(s):** 10 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2028
Trial Design	Open-label, single group assignment
Population	N=545 (estimated); completed 30 months of the blinded study treatment in Study AG10-301 (NCT03860935) and the Study AG10-301 Month 30 visit including assessments and procedures; aged 18 – 90 years
Intervention(s)	Acoramidis HCl 800mg oral tablet administered twice daily
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Incidence of treatment-emergent Adverse Events [safety and tolerability] [time frame: 60 months].

	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ATTRibute-CM;** NCT03860935; **EudraCT** 2018-004280-32; A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects With Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial) **Phase III** – Active, not recruiting **Location(s):** 9 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2023
Trial Design	Randomised, quadruple-masked, parallel assignment
Population	N=632 (actual); established diagnosis of ATTR-CM with either wild-type TTR or variant TTR genotype; have a history of heart failure; aged 18 – 90 years
Intervention(s)	Acoramidis HCl 800mg oral tablet administered twice daily
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • 6 Minute Walk Test (6MWT) at Month 12 [time frame: at Month 12] • A hierarchical combination of all-cause mortality, frequency of cardiovascular-related hospitalisation, and change from baseline to Month 30 of treatment in the total distance walked in 6 minutes [time frame: 30 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03536767; An Open-Label Extension and Safety Monitoring Study of Patients With Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201 **Phase II** – active, not recruiting **Location(s):** USA **Primary completion date:** July 2027
Trial Design	Open-label, single group assignment
Population	N=47 (actual)[13]; completed participation in study AG10-201; aged 18 – 90 years
Intervention(s)	Acoramidis HCl 800mg oral tablet administered twice daily
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures:

	• Assessment of long-term safety and tolerability: Incidence of each treatment-emergent adverse events [time frame: up to 60 Months or study completion by recommendation from safety monitoring committee]. See trial record for full list of other outcomes.
Results (efficacy)	Median decline in N-terminal Pro-brain natriuretic peptide (NT-proBNP) levels, normalisation of serum TTR, and sustained stabilisation of TTR were observed.[13]
Results (safety)	Long term treatment with acoramidis was generally well tolerated.[13]

Trial	NCT03458130; A Phase 2, Randomized, Placebo-controlled, Dose-ranging Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AG10 in Patients With Symptomatic Transthyretin Amyloid Cardiomyopathy **Phase II** – completed **Location(s):** USA **Study completion date:** October 2018
Trial Design	Randomised, quadruple-masked, parallel assignment
Population	N=49 (actual); have an established diagnosis of ATTR-CM with either wild-type transthyretin or a variant transthyretin genotype; have a history of heart failure; aged 18 – 90 years
Intervention(s)	Acoramidis Low Dose Arm: acoramidis HCl 400mg tablets twice daily for 28 days Acoramidis High Dose Arm: acoramidis HCl 800mg tablets twice daily for 28 days
Comparator(s)	Placebo
Outcome(s)	Primary outcome measures [time frame: baseline to Day 28]: • Change in Diastolic Blood Pressure (post dose) • Change in Heart Rate (post dose) • Change in Respiratory Rate (post dose) • Change in Temperature • Change in Systolic Blood Pressure See trial record for full list of other outcomes.
Results (efficacy)	Acoramidis treatment increased serum TTR levels from baseline and brought those levels to within the normal range in all subjects, both mutant and wild-type. This included subjects whose baseline levels were markedly below the normal range. Treatment with acoramidis HCl 400mg and 800mg twice daily resulted in mean increases in serum TTR concentration of 29% and 34% in the subgroup of wild-type ATTR-CM subjects, respectively, suggesting a potentially larger treatment effect than was observed with the other stabilisers.[4]
Results (safety)	Acoramidis was generally well-tolerated. The proportion of subjects who experienced AEs was 88%, 63%, and 69% of subjects administered placebo and 400mg and 800mg acoramidis, respectively. Most AEs were mild to moderate in severity in both the placebo and active treatment groups. The most observed AEs, occurring in four or more subjects across all treatment groups including placebo, were atrial fibrillation, constipation, diarrhoea, and muscle spasms. There were no

	clinically important changes or trends observed in safety laboratory tests that were inconsistent with the underlying disease (e.g., elevations in NT-proBNP or troponin I), nor were there any clinically important changes from baseline electrocardiography findings in the study.[4]

Estimated Cost

The cost of acoramidis is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for cardiology: Inherited cardiac conditions (All ages). A09/S/c.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages). E13/S(HSS)/c.

Other Guidance

- Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. European Journal of Heart Failure. 2021.[14]
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Additional Information

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