

RESEARCH MONOGRAPH . COMPOUND PROFILE

Acoramidis

A fluorinated benzoic acid derivative engineered to replicate the enthalpy-driven transthyretin stabilization of the protective T119M genetic variant, approved for transthyretin amyloid cardiomyopathy following a positive Phase 3 trial demonstrating reductions in all-cause mortality and cardiovascular hospitalization.

DOCUMENT	KDC-MN-1660
ISSUED	2026-05-22
REVISION	1.0
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COMPOUND CLASS	Selective transthyretin tetramer kinetic stabilizer designed to mimic the naturally occurring T119M protective variant

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ABSTRACT

Acoramidis (AG10) is a potent, selective, orally bioavailable small-molecule kinetic stabilizer of the transthyretin (TTR) tetramer, approved in the United States, European Union, United Kingdom, and Japan for the treatment of cardiomyopathy caused by wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM). The compound was rationally designed to replicate the molecular mechanism of the naturally occurring T119M variant of TTR, a protective mutation that stabilizes the tetramer against the rate-limiting dissociation step that initiates amyloid fibril formation. Structurally, acoramidis is a 3,5-dimethylpyrazole linked through a propyloxy tether to a 4-fluorobenzoic acid; the pyrazole ring forms two hydrogen bonds with serine 117 and serine 117 prime residues at the floor of the thyroxine binding pocket, replicating the inter-dimer contact created by the threonine-to-methionine substitution in T119M carriers. This enthalpy-driven binding mechanism (binding enthalpy of negative 13.6 kilocalories per mole, compared to negative 5.0 kilocalories per mole for tafamidis) underpins the high selectivity of acoramidis for TTR over albumin and its capacity to achieve greater than 90 percent tetramer stabilization across the entire dosing interval at steady state. The clinical development program for acoramidis established pharmacokinetic parameters favorable for twice-daily oral dosing: rapid absorption (time to peak concentration less than one hour), terminal elimination half-life of approximately 25 hours, metabolism principally by UGT-mediated glucuronidation rather than cytochrome P450 enzymes, and renal elimination of conjugated metabolites. The pivotal Phase 3 ATTRIBUTE-CM trial randomized 632 patients with wild-

type or hereditary ATTR-CM to acoramidis 800 milligrams (as the hydrochloride salt) twice daily or placebo for 30 months. On the primary hierarchical endpoint (a four-component analysis of all-cause mortality, cardiovascular-related hospitalization, NT-proBNP change, and six-minute walk distance), acoramidis demonstrated a win ratio of 1.8 (95 percent confidence interval 1.4 to 2.2; P less than 0.001). The time-to-event composite of all-cause mortality or first cardiovascular hospitalization favored acoramidis with a hazard ratio of 0.64 (95 percent confidence interval 0.50 to 0.83; P equals 0.0008), with Kaplan-Meier curves separating at three months and benefit sustained through 42 months of follow-up in the open-label extension. A cardiac magnetic resonance substudy demonstrated stabilization of left ventricular mass and improvement of ejection fraction in the acoramidis arm relative to progressive deterioration in placebo recipients. The adverse event profile was similar to placebo; diarrhea (11.6 versus 7.6 percent) and gout (10.9 versus 8.1 percent) were the most frequent treatment-emergent events occurring at higher rates with acoramidis. This monograph reviews the chemistry, synthesis, and rational design of acoramidis; the enthalpy-driven TTR stabilization mechanism characterized through isothermal titration calorimetry and X-ray crystallography; the complete human pharmacokinetic profile; preclinical pharmacology in rodent and canine models; the clinical evidence base from Phase 1 through Phase 3 and the open-label extension; sourcing and quality considerations for research applications; reconstitution and handling; metabolic and pharmacodynamic interactions; the adverse event and safety profile; and a comparative assessment of five transthyretin-directed therapies (tafamidis, diflunisal, patisiran, vutrisiran, and eplontersen) against acoramidis on five competency standards.

Acoramidis is a prescription medicine in its approved jurisdictions and is available as a research-grade preparation for investigational applications outside the approved indication. Investigators should obtain analytical confirmation of identity and purity on every research-grade lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Acoramidis.

Brand names: Attruby (United States; BridgeBio Pharma), Beyontra (European Union; BridgeBio Pharma) [1, 2].

Development code: AG10 (the designation derives from "Alhamadsheh-Graef molecule 10," reflecting the two co-inventors of the compound) [3].

Chemical Abstracts Service registry numbers: 1446711-81-4 (acoramidis free acid); 2242751-53-5 (acoramidis hydrochloride salt) [4].

International Union of Pure and Applied Chemistry name: 3-[3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid [4].

Molecular formula: C₁₅H₁₇FN₂O₃ (free acid); C₁₅H₁₈ClFN₂O₃ (hydrochloride salt) [4].

Molecular weight: 292.31 g/mol (free acid) [4].

1.2 Structural class and chemistry

Acoramidis belongs to the structural class of fluorinated benzoic acid derivatives containing a pyrazole heterocycle. The molecule comprises three principal pharmacophoric elements: a 3,5-dimethyl-1H-pyrazole ring, which forms the critical hydrogen-bonding contacts with the serine 117 residues at the floor of the transthyretin thyroxine binding pocket; a three-carbon propyloxy linker that spans the distance between the pyrazole and aryl pharmacophores; and a 4-fluorobenzoic acid, whose carboxylate group forms electrostatic salt-bridge interactions with the lysine 15 and lysine 15 prime residues at the mouth of the binding pocket, while the fluorine atom occupies halogen binding pocket 1 of the TTR tetramer [1, 5].

The compound does not contain a chiral center and is supplied as a single chemical entity without stereochemical complexity. The free acid form is the pharmacologically active species; the hydrochloride salt is used in the marketed formulation

for enhanced solid-state stability and reproducible oral absorption. The free acid equivalent of the approved 800 milligram hydrochloride dose is 712 milligrams [2].

The structural design of acoramidis was guided by the X-ray crystal structure of the T119M protective variant of human TTR and by structure-activity relationship optimization from a high-throughput screening hit [1, 5]. The compound was purpose-built to interact with the bottom of the T4 binding pocket, a region that tafamidis, diflunisal, and tolcapone do not efficiently engage, and that the T119M threonine-to-methionine substitution modifies through creation of a direct inter-subunit hydrogen bond between serine 117 residues across the dimer-dimer interface [5].

1.3 Synthesis

The synthesis of AG10 as described by Penchala et al. (2013) proceeds through a convergent route [1]. The 3,5-dimethyl-1H-pyrazole ring is prepared or sourced commercially. The propyloxy linker is installed by O-alkylation of 3-hydroxy-4-fluorobenzoic acid (or its protected ester) with 1,3-dibromopropane under basic conditions (potassium carbonate, dimethylformamide) to yield the bromopropyloxy intermediate [6]. The pyrazole is then coupled to the terminal bromide of the linker under similar alkylation conditions. Final deprotection of the benzoic acid ester, if applicable, and purification by recrystallization yield acoramidis as a white crystalline solid. The hydrochloride salt is prepared by treatment of the free acid with hydrochloric acid in an appropriate solvent followed by recrystallization. The synthesis is scalable and has been adapted for commercial manufacturing at good manufacturing practice (GMP) grade for the marketed formulation.

2. Abstract

The abstract appears in the YAML frontmatter above and is not repeated as a body section.

3. Discovery and Development History

3.1 Origin

Acoramidis originated from a collaboration between Mamoun M. Alhamadsheh, a pharmaceutical chemist at the University of the Pacific, and Isabella A. Graef, a physician-scientist then at Stanford University. The program began with a high-throughput screen for small molecules that bind and stabilize the transthyretin tetramer, motivated by the recognition that TTR tetramer dissociation is the rate-limiting step in the amyloidogenic cascade that produces ATTR amyloidosis [7]. The critical insight that shaped AG10's design was the observation that the naturally occurring T119M variant of TTR, carried by approximately 1 percent of the Portuguese population, confers protection against familial amyloid polyneuropathy even in trans-heterozygous carriers of pathogenic mutations such as V30M. The T119M substitution stabilizes the tetramer by creating a direct hydrogen bond between serine 117 residues across the dimer-dimer interface [1, 5]. Alhamadsheh designed AG10 to replicate this inter-subunit bridging mechanism through the pyrazole ring, using structural insights from co-crystal structures of TTR with known ligands [7].

3.2 Academic development and founding of Eidos Therapeutics

In 2012, Alhamadsheh and Graef entered the Stanford SPARK Translational Research Program (Stanford Program for Advancing Research and Knowledge), which provided mentorship and resources for translating the academic discovery toward clinical candidacy [7]. In 2013, the first peer-reviewed characterization of AG10 was published in the Proceedings of the National Academy of Sciences, demonstrating that AG10 inhibits amyloidogenesis and cellular toxicity of the V122I-TTR variant (the most common cardiac-tropic pathogenic mutation, carried by 3 to 4 percent of African Americans) at nanomolar binding affinity and with superior selectivity for TTR over albumin compared to tafamidis [1]. In the same year, Alhamadsheh and Graef co-founded Eidos Therapeutics to advance AG10 into clinical development. Eidos completed a public offering in 2018 that provided the capital for the Phase 2 and Phase 3 clinical programs [7].

3.3 Clinical development milestones

The first-in-human Phase 1 study was initiated in 2017 and enrolled 56 healthy adult volunteers in single ascending dose and multiple ascending dose cohorts; results demonstrating near-complete TTR stabilization at the 800 milligram twice-daily dose were published by Fox et al. in 2019 [3]. The Phase 2 randomized, double-blind, placebo-controlled trial enrolled 49 patients with symptomatic ATTR-CM (wild-type and hereditary) and demonstrated 92 percent TTR stabilization at trough at the 800 milligram dose over 28 days; results were published by Judge et al. in the Journal of the American College of Cardiology in 2019 [8]. The pivotal Phase 3 ATTRIBUTE-CM trial (NCT03860935) enrolled 632 patients beginning in 2019 and reported positive primary endpoint results at 30 months in a publication by Gillmore et al. in the New England Journal of Medicine in January 2024 [9].

3.4 Acquisition and regulatory approval

In 2021, BridgeBio Pharma acquired Eidos Therapeutics, bringing acoramidis under BridgeBio's rare disease portfolio. On November 22, 2024, the United States Food and Drug Administration approved acoramidis (Attruby) for the treatment of adults with cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis, at a recommended dose of 712 milligrams (free acid equivalent) twice daily [2]. The compound subsequently received marketing authorization in the European Union (as Beyontra), the United Kingdom, and Japan for the same indication [10]. Additional clinical programs are ongoing: ATTRIBUTE-PN (NCT04882735) for transthyretin amyloid polyneuropathy, ACT-EARLY (NCT06563895) for asymptomatic carriers of pathogenic TTR variants, and real-world evidence studies [10].

4. Molecular Pharmacology

4.1 Transthyretin biology and the amyloidogenic cascade

Transthyretin is a 55-kilodalton homotetrameric protein synthesized primarily in the liver and the choroid plexus. Each monomer consists of 127 amino acids folded into a beta-sheet-rich structure; four monomers assemble into a dimer-of-dimers tetramer that circulates in plasma at concentrations of approximately 20 to 40 milligrams per deciliter [11, 12]. The tetramer contains two thyroxine (T4) binding sites located at the dimer-dimer interface; in vivo, these sites are largely unoccupied because thyroxine-binding globulin carries the majority of circulating thyroxine [5]. The biological functions of TTR include transport of thyroxine and, through a ternary complex with retinol-binding protein 4, transport of retinol (vitamin A).

The amyloidogenic cascade of ATTR amyloidosis begins with dissociation of the TTR tetramer into its constituent monomers, the rate-limiting step [1, 5]. Dissociated monomers undergo partial unfolding, exposing hydrophobic surfaces that drive aggregation first into soluble oligomers and subsequently into insoluble amyloid fibrils. These fibrils deposit in target tissues (heart, peripheral nerves, gastrointestinal tract, carpal tunnel ligaments, vitreous humor) and cause progressive organ dysfunction. In ATTR-CM, infiltration of the myocardium by amyloid fibrils produces restrictive cardiomyopathy, heart failure, conduction system disease, and death [11, 12].

Wild-type TTR (ATTRwt) causes senile cardiac amyloidosis, estimated to affect 10 to 25 percent of heart failure with preserved ejection fraction patients over age 80. More than 130 pathogenic missense variants cause hereditary ATTR (ATTRv); V122I (present in approximately 3 to 4 percent of African Americans) and T60A are the most prevalent cardiac-tropic variants [11, 12].

4.2 Mechanism of TTR kinetic stabilization by acoramidis

Acoramidis binds to the thyroxine binding sites of the TTR tetramer and dramatically slows the rate of tetramer dissociation, thereby arresting the amyloidogenic cascade at its rate-limiting step [1, 5]. The compound was designed to replicate the inter-dimer stabilization mechanism of the T119M protective variant.

The X-ray crystal structure of AG10 bound to V122I-TTR, solved at 1.18-angstrom resolution (Protein Data Bank identifier 4HIQ), reveals the molecular basis of this mimicry [1, 5]. The 3,5-dimethylpyrazole ring of AG10 inserts into the inner cavity of the T4 binding pocket and forms two direct hydrogen bonds with the hydroxyl side chains of serine 117 (S117) and serine 117 prime (S117') of adjacent monomers across the dimer-dimer interface, at a distance of approximately 2.8 angstroms [5]. In the wild-type TTR tetramer without a stabilizing ligand, these two S117 residues are separated by approximately 6.0 angstroms and do not interact directly; in the T119M variant, the methionine side chain creates a direct inter-residue contact that closes this distance to approximately 4.8 angstroms [5]. AG10 achieves a comparable dimer-dimer distance of approximately 4.66 angstroms [5]. At the outer mouth of the binding pocket, the carboxylate group of the fluorobenzoic acid moiety forms electrostatic salt bridges with the epsilon-amino groups of lysine 15 and lysine 15 prime, while the fluorine atom occupies halogen binding pocket 1 [1, 5].

4.3 Binding thermodynamics and comparison to other stabilizers

Miller et al. (2018) characterized the binding thermodynamics of AG10 and three comparator TTR stabilizers by isothermal titration calorimetry (ITC) [5]. The key finding is that AG10 binding to TTR is dominated by a large favorable binding enthalpy (negative 13.6 kilocalories per mole), whereas tafamidis binding, despite a similar overall free energy of binding, is predominantly entropy-driven. The thermodynamic parameters are:

AG10: dissociation constant (Kd) 4.8 plus or minus 1.9 nanomolar; binding enthalpy (ΔH) negative 13.6 kilocalories per mole; free energy of binding (ΔG) negative 11.34 kilocalories per mole; entropy contribution ($T\Delta S$) negative 2.26 kilocalories per mole [5].

Tafamidis: Kd 4.4 plus or minus 1.3 nanomolar; ΔH negative 5.0 kilocalories per mole; ΔG negative 11.39 kilocalories per mole; $T\Delta S$ positive 6.39 kilocalories per mole [5].

Diflunisal: Kd 407 plus or minus 35 nanomolar; ΔH negative 8.38 kilocalories per mole; ΔG negative 8.72 kilocalories per mole; $T\Delta S$ positive 0.34 kilocalories per mole [5].

Tolcapone: Kd 20.6 plus or minus 3.7 nanomolar; deltaH negative 10.1 kilocalories per mole; deltaG negative 10.5 kilocalories per mole; TdeltaS positive 0.4 kilocalories per mole [5].

The correlation between binding enthalpy and TTR stabilization potency was strong (R-squared equals 0.98), supporting the thesis that the enthalpy-driven hydrogen-bonding mechanism of AG10 is the molecular determinant of its superior stabilization in serum-based assays [5].

4.4 TTR stabilization in human serum

In Western blot assays of acid-mediated TTR denaturation (pH 4.0, 72 hours) in pooled human serum, AG10 at 10 micromolar (approximating the steady-state trough plasma concentration at the 800 milligram twice-daily dose) preserved 95.4 plus or minus 4.8 percent of TTR in the tetrameric state, compared to 41.5 plus or minus 4.6 percent for tafamidis at 20 micromolar (approximating its clinical steady-state concentration), 68.4 plus or minus 5.1 percent for tolcapone at 20 micromolar, and 24.2 plus or minus 2.3 percent for diflunisal at 200 micromolar [5].

In serum from patients heterozygous for V122I/wild-type TTR, AG10 at 10 micromolar achieved 108.3 plus or minus 5.2 percent tetramer stabilization (values above 100 percent reflect methodological variability); tafamidis at 20 micromolar achieved 31.1 plus or minus 4.8 percent stabilization in serum from homozygous V122I patients, a statistically significant difference [1].

4.5 Selectivity

AG10 demonstrates high selectivity for binding TTR over albumin and other abundant serum proteins. In gel filtration and dialysis experiments, 7.8 plus or minus 0.1 micromolar of AG10 was bound to albumin versus 18.8 plus or minus 2.1 micromolar of tafamidis, indicating that tafamidis binds albumin more avidly than AG10 [5]. In a competition assay with a covalent TTR probe, AG10 permitted only 3.1 plus or minus 2.9 percent probe binding to TTR (indicating near-complete occupancy), compared to 70.5 plus or minus 1.4 percent probe binding with tafamidis, consistent with substantially greater TTR selectivity for AG10 in the serum milieu [1].

Addition of albumin, transferrin, fibrinogen, or immunoglobulin G to the assay system did not reduce AG10's TTR occupancy (greater than 97 percent maintained), whereas albumin reduced tafamidis TTR occupancy from 68.2 to 41.5 percent [5].

These selectivity differences contribute to the higher functional TTR stabilization observed for AG10 at clinical plasma concentrations.

4.6 Methodological considerations

The comparative advantage of AG10 over tafamidis varies with the assay system. Powers et al. (2025) noted that when binding and potency are measured using the subunit exchange methodology (considered the gold-standard kinetic assay), "tafamidis and acoramidis exhibited similar potency and binding affinity...at the plasma concentrations achieved by their standard dosages" [14]. This finding does not contradict the serum Western blot and FPE data but highlights that the degree of differentiation depends on assay conditions, particularly the influence of albumin competition and the thermodynamic versus kinetic framing of stabilization [14]. Investigators interpreting the relative potency of these stabilizers should consider the assay system and the clinical relevance of each measurement.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Acoramidis is rapidly absorbed after oral administration. In the Phase 1 study in healthy volunteers, median time to peak plasma concentration (T_{max}) ranged from 0.75 to 1 hour across dose levels in the fasted state [3]. After a single 300 milligram fasted dose, maximum plasma concentration (C_{max}) was 4,510 nanograms per milliliter and the area under the plasma concentration-time curve from zero to 24 hours (AUC₀₋₂₄) was 29,300 nanogram-hours per milliliter [3]. At steady state (800 milligrams every 12 hours for 12 days), C_{max} was 13,700 nanograms per milliliter and AUC over the dosing interval was 47,200 nanogram-hours per milliliter, with mean accumulation ratios of 1.3 to 1.6 [3].

A food-effect substudy at the 300 milligram dose demonstrated that a high-fat meal increased AUC from 52,800 to 65,100 nanogram-hours per milliliter, decreased C_{max} from 4,510 to 3,040 nanograms per milliliter, and delayed T_{max} from 0.75 to 1.5 hours [3]. These differences were not considered clinically meaningful, and the compound may be administered without regard to food [2, 3].

5.2 Distribution

Acoramidis is approximately 96 percent protein-bound in human plasma, with the majority of binding to its pharmacological target, transthyretin [2, 14]. The apparent volume of distribution at steady state is approximately 654 liters, indicating extensive tissue distribution [2].

5.3 Metabolism

Acoramidis is metabolized primarily through glucuronidation mediated by uridine diphosphate-glucuronosyltransferase (UGT) enzymes, specifically UGT1A9, UGT1A1, and UGT2B7 [2, 11]. The major circulating species is the acoramidis glucuronide conjugate. The primary metabolite (designated AG10-AG) retains only 24 to 34 percent of the TTR-stabilizing activity of the parent compound [3].

Acoramidis is not metabolized by cytochrome P450 enzymes CYP2C8, CYP2C19, CYP2D6, or CYP3A4/5, and does not induce CYP1A2 or CYP2B6 [2]. This CYP-independent metabolic profile confers a favorable drug interaction profile compared to compounds metabolized through CYP-dependent pathways.

5.4 Elimination

The terminal elimination half-life of acoramidis is approximately 25 hours, as characterized in the Phase 1 study [3]. The effective half-life (the half-life that governs accumulation with repeated dosing) is approximately 6 hours, reflecting the distribution phase and the contribution of target-mediated disposition through TTR binding [14]. Renal clearance was 1,750 milliliters per hour in the Phase 1 multiple ascending dose cohort [3].

Elimination occurs through both renal and fecal routes: approximately 68 percent of an administered dose is recovered in urine (less than 10 percent as unchanged acoramidis) and approximately 32 percent in feces (approximately 15 percent as unchanged acoramidis) [2].

5.5 Drug interactions

Acoramidis is a substrate of organic anion transporter 1 (OAT1) and breast cancer resistance protein (BCRP). It inhibits OAT1 and OAT3 in vitro but does not produce clinically significant increases in exposure to OAT1 substrates (adefovir) or OAT3 substrates (oseltamivir carboxylate) at the therapeutic dose [2]. Acoramidis does not inhibit MATE1, MATE2-K, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, P-glycoprotein, or the bile salt export pump [2].

Acoramidis may increase plasma concentrations of CYP2C9 substrates; monitoring for signs of toxicity of concomitant CYP2C9 substrates (warfarin, phenytoin, celecoxib) is recommended [2]. Coadministration with UGT inducers may decrease acoramidis exposure [2].

5.6 Special populations

Renal impairment does not significantly affect acoramidis pharmacokinetics, and no dose adjustment is required [2, 3]. Food does not produce a clinically significant effect on exposure [3]. Pharmacokinetic data in hepatic impairment, pediatric pop-

ulations, and pregnancy are limited; the compound is approved for adult use only [2].

6. Preclinical Pharmacology

6.1 In vitro TTR stabilization

The foundational in vitro characterization of AG10 was published by Penchala et al. (2013) [1]. In fluorescence polarization (FP) competition assays against a fluorescent TTR probe, AG10 displaced the probe with an apparent binding constant (K_{app}) of 193 nanomolar, compared to 247 nanomolar for tafamidis [1]. By isothermal titration calorimetry, AG10 bound TTR with a first-site dissociation constant (K_{d1}) of 4.8 nanomolar and a second-site K_d (K_{d2}) of 314 nanomolar, reflecting the positive cooperativity characteristic of the two T4 binding sites [1].

In acid-mediated denaturation assays (pH 4.0, 72 hours), AG10 at 10 micromolar preserved 97.6 plus or minus 9.4 percent of TTR in the tetrameric state in human serum, compared to 49.4 plus or minus 4.3 percent for tafamidis at the same concentration [1]. At 5 micromolar, AG10 preserved 74.9 plus or minus 11.5 percent compared to 37.8 plus or minus 3.3 percent for tafamidis [1]. These results established that AG10 achieves substantially greater TTR stabilization than tafamidis at equimolar concentrations in the serum milieu, where competition with albumin and other serum proteins is present.

6.2 Cellular toxicity protection

In the AC16 human cardiomyocyte cell line, amyloidogenic V122I-TTR produces concentration-dependent proteotoxicity that models the cellular injury occurring in ATTR cardiomyopathy. Penchala et al. (2013) demonstrated that AG10 at 8 micromolar protected AC16 cardiomyocytes from V122I-TTR-mediated cytotoxicity, as did tafamidis at the same concentration [1]. This assay confirmed that the TTR stabilization observed in cell-free assays translates to cytoprotection in a cardiomyocyte model relevant to the disease indication.

6.3 X-ray crystallography

The crystal structures of AG10 bound to V122I-TTR (PDB 4HIQ, 1.18-angstrom resolution) and tafamidis bound to V122I-TTR (PDB 4HIS, 1.20-angstrom resolution) were solved by Penchala et al. (2013) and analyzed in detail by Miller et al. (2018) [1, 5]. These structures revealed the T119M-mimetic hydrogen bonding between the AG10 pyrazole and the S117/S117' hydroxyl groups and the absence of equivalent inter-subunit contacts in the tafamidis-TTR structure. The crystallographic data provided the structural rationale for the enthalpy-driven binding and the selectivity differences between the two stabilizers.

6.4 In vivo pharmacology in rodents

Penchala et al. (2013) reported that AG10 demonstrated oral bioavailability in rodents with excellent chemical and metabolic stability [1]. A 28-day repeat-dose toxicology study in Wistar rats at 50 milligrams per kilogram per day (achieving a C_{max} of approximately 40 micromolar, roughly four-fold above the human therapeutic plasma concentration) showed no signs of toxicity, no mortality, and no abnormal clinical chemistry or histopathology findings [1]. The favorable safety margin in the rat supported advancement to first-in-human studies.

6.5 In vivo pharmacology in dogs

Miller et al. (2018) characterized the pharmacokinetic-pharmacodynamic relationship of oral AG10 in beagle dogs over seven days of dosing [5]. TTR occupancy was measured by the fluorescent probe exclusion (FPE) assay at trough (C_{min}) and peak (C_{max}) plasma concentrations:

At 50 milligrams per kilogram: approximately 81 percent TTR occupancy at trough, greater than 97 percent at peak [5].

At 100 milligrams per kilogram: approximately 89 percent at trough, greater than 97 percent at peak [5].

At 200 milligrams per kilogram: approximately 94 percent at trough, greater than 97 percent at peak [5].

Circulating plasma concentration of AG10 correlated well with TTR occupancy, establishing a quantitative PK-PD relationship that informed human dose selection. The 800 milligram twice-daily dose in humans was selected to achieve greater than

90 percent TTR occupancy throughout the dosing interval, analogous to the 100 to 200 milligram per kilogram dose range in dogs [3, 5].

6.6 Translational validity

The TTR stabilization mechanism is directly conserved across species: human TTR, canine TTR, and rodent TTR share the T4 binding pocket architecture, and AG10 binds all species' TTR at the same site. The in vitro assays used human serum and human TTR; the crystal structures used human V122I-TTR; and the PK-PD relationship in dogs was calibrated against human target engagement parameters. The translational bridge from preclinical to clinical TTR stabilization was therefore unusually strong, and the Phase 1 clinical results confirmed near-complete TTR stabilization at the predicted dose [3].

7. Clinical Evidence Base

The clinical evidence for acoramidis is presented for research and educational purposes. The compound is approved as a prescription medicine for ATTR-CM in several jurisdictions; investigators using the compound for research outside the approved indication should operate under appropriate regulatory oversight and informed consent.

7.1 Phase 1: first-in-human study in healthy volunteers

Fox et al. (2020) reported a randomized, double-blind, placebo-controlled Phase 1 study of AG10 in 56 healthy adult volunteers conducted in two parts [3]. Part A (single ascending dose) enrolled four cohorts of eight subjects each (six active, two placebo per cohort) at doses of 50, 150, 300, and 800 milligrams. Part B (multiple ascending dose) enrolled three cohorts of eight subjects each (six active, two placebo) at doses of 100, 300, and 800 milligrams every 12 hours for 12 days [3].

At the 800 milligram every-12-hour steady-state dose, mean TTR stabilization by the FPE assay was 92 percent at the 12-hour trough, consistent with near-complete target engagement across the entire dosing interval [3]. Serum TTR concentrations increased by approximately 60 percent from baseline by day 12, reflecting the pharmacodynamic consequence of stabilizing the tetramer against clearance [3]. No dose-limiting toxicities, serious adverse events, or deaths were observed. Adverse events occurred in 29 percent of active-treated subjects versus 25 percent of placebo recipients in Part A and 44 percent versus 50 percent in Part B, with no dose-dependent pattern [3]. The most common events (each reported in no more than two subjects) were dry mouth, headache, upper respiratory infection, and dizziness [3]. No clinically important changes in safety laboratory tests or electrocardiographic parameters were observed [3].

7.2 Phase 2: transthyretin stabilization in symptomatic ATTR-CM

Judge et al. (2019) reported a randomized, double-blind, placebo-controlled Phase 2 trial (NCT03458130) enrolling 49 patients with symptomatic ATTR-CM (wild-type or hereditary) across three treatment arms: AG10 400 milligrams twice daily, AG10 800 milligrams twice daily, or placebo for 28 days [8]. The primary pharmacodynamic endpoint was TTR stabilization measured by FPE.

At the 800 milligram dose, TTR stabilization at trough was 92 plus or minus 10 percent and at peak was 96 plus or minus 9 percent (both P less than 10 to the negative 12th power versus placebo) [8]. Mean serum TTR increased by 36 plus or minus 21 percent at the 400 milligram dose and 51 plus or minus 38 percent at the 800 milligram dose [8]. At baseline, 80 percent of patients with hereditary ATTR and 33 percent of patients with wild-type ATTR had below-normal serum TTR concentrations; AG10 treatment at 800 milligrams restored serum TTR to the normal range in all subjects [8]. The compound was well tolerated; no significant safety signals were observed over the 28-day treatment period [8].

7.3 Phase 3: ATTRibute-CM pivotal trial

Gillmore et al. (2024) published the results of the ATTRibute-CM trial (NCT03860935), a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study of acoramidis in ATTR-CM [9]. A total of 632 patients with wild-type (n equals 571) or hereditary (n equals 61) ATTR-CM were randomized in a 2:1 ratio to acoramidis hydrochloride 800 milligrams twice daily or matching placebo, with a 30-month treatment period. The analysis population comprised 611 subjects (409 acoramidis, 202 placebo) [9, 10].

The primary endpoint was a hierarchical four-component analysis using the Finkelstein-Schoenfeld method, incorporating (in descending priority) all-cause mortality, frequency of cardiovascular-related hospitalization, change in NT-proBNP, and change in six-minute walk distance at 30 months [9]. Acoramidis demonstrated a win ratio of 1.8 (95 percent confidence interval 1.4 to 2.2; P less than 0.001) [9].

Key secondary and pre-specified endpoints included:

Composite of all-cause mortality or first cardiovascular hospitalization: 35.9 percent acoramidis versus 50.5 percent placebo; hazard ratio 0.64 (95 percent confidence interval 0.50 to 0.83; P equals 0.0008) [10].

First cardiovascular hospitalization alone: 26.7 percent versus 42.6 percent; hazard ratio 0.60 (95 percent confidence interval 0.45 to 0.80; P equals 0.0005) [10].

Annualized cardiovascular hospitalization rate: 0.22 acoramidis versus 0.45 placebo; relative risk ratio 0.50 (95 percent confidence interval 0.36 to 0.70; P less than 0.0001); number needed to treat of 5 [10, 15].

Six-minute walk distance: least-squares mean difference of 39.6 meters in favor of acoramidis (95 percent confidence interval 21.1 to 58.2; P less than 0.001) [9, 14].

Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score: least-squares mean difference of 9.94 points in favor of acoramidis (95 percent confidence interval 6.0 to 13.9; P less than 0.001) [9, 14].

NT-proBNP: ratio of geometric mean fold change (acoramidis to placebo) at month 30 was 0.55 (95 percent confidence interval 0.48 to 0.64; P less than 0.001) [9, 14].

All-cause mortality alone: hazard ratio 0.77 (95 percent confidence interval 0.54 to 1.10; P equals 0.154), a numerically favorable trend that did not reach statistical significance at the 30-month timepoint [15].

Kaplan-Meier curves for the composite endpoint separated at month 3, indicating early clinical benefit [10].

7.4 Subgroup analysis: wild-type versus variant ATTR-CM

Alexander et al. (2025) published a pre-specified subgroup analysis of ATTRibute-CM stratified by ATTR-CM genotype [13]. In the wild-type subgroup (n equals 552; 370 acoramidis, 182 placebo), the win ratio for the primary hierarchical endpoint was 1.8 (95 percent confidence interval 1.40 to 2.21; P less than 0.001) and the hazard ratio for all-cause mortality or first cardiovascular hospitalization at month 30 was 0.69 (95 percent confidence interval 0.52 to 0.90; P equals 0.007) [13]. In the variant subgroup (n equals 59; 39 acoramidis, 20 placebo), the win ratio was 2.5 (95 percent confidence interval 1.30 to 4.91; P equals 0.006) and the composite hazard ratio was 0.41 (95 percent confidence interval 0.21 to 0.81; P equals 0.01) [13].

By month 42 (open-label extension), all-cause mortality was reduced in both subgroups: hazard ratio 0.70 (95 percent confidence interval 0.50 to 0.98; P equals 0.04) in wild-type and 0.41 (95 percent confidence interval 0.19 to 0.93; P equals 0.03) in variant [13]. The six-minute walk distance treatment effect was 34.4 meters (P equals 0.001) in wild-type and 86.7 meters (P equals 0.005) in variant [13]. KCCQ-OS differences were 8.8 points (P less than 0.001) and 20.3 points (P equals 0.002), respectively [13]. No significant heterogeneity of treatment effect was detected for any endpoint (interaction P values greater than 0.05) [13].

7.5 Open-label extension

Judge et al. (2025) reported the initial results from the open-label extension (OLE) of ATTRIBUTE-CM, in which 389 eligible participants (263 randomized to continuous acoramidis, 126 from placebo switched to acoramidis) continued acoramidis 800 milligrams hydrochloride twice daily for an additional 12 months beyond the 30-month randomized period (42 months total from baseline) [16].

At month 42, the hazard ratio for all-cause mortality or first cardiovascular hospitalization comparing continuous acoramidis to placebo-to-acoramidis was 0.57 (95 percent confidence interval 0.46 to 0.72; P less than 0.0001) [16]. All-cause mortality was 23.0 percent in the continuous acoramidis group versus 34.7 percent in the placebo-to-acoramidis group; hazard ratio 0.64 (95 percent confidence interval 0.47 to 0.88; P equals 0.006) [16]. Cardiovascular hospitalization occurred in 31.5 percent versus 53.5 percent; hazard ratio 0.53 (95 percent confidence interval 0.41 to 0.69; P less than 0.0001) [16].

NT-proBNP geometric mean fold change from baseline at month 42 was 1.10 in the continuous acoramidis group versus 2.29 in the placebo-to-acoramidis group [16]. The six-minute walk distance declined by 24.5 plus or minus 5.33 meters and the KCCQ-OS declined by 4.0 plus or minus 1.15 points in the continuous arm at month 42, reflecting the natural progressive course of ATTR-CM even with treatment but with substantially less decline than observed in the placebo period [16].

Serum TTR increased by 9.1 plus or minus 0.34 milligrams per deciliter from baseline at month 30 in the continuous arm; participants who switched from placebo to acoramidis showed a rapid pharmacodynamic response, with serum TTR rising from 1.3 plus or minus 0.55 milligrams per deciliter at month 30 (still on placebo) to 7.4 plus or minus 0.55 milligrams per deciliter at month 31 (one month

after switch) [16]. These data demonstrate that the pharmacodynamic effect of acoramidis is reversible and that delayed initiation of treatment is associated with incomplete recovery of the clinical trajectory lost during the placebo period [16].

7.6 Cardiac magnetic resonance substudy

Razvi et al. (2024) reported the ATTRibute-CM cardiac magnetic resonance (CMR) substudy in 52 participants (47 male; mean age 74.3 years) who underwent serial CMR at baseline, 12 months, 24 months, and 30 months [17]. In the acoramidis arm, indexed left ventricular mass remained stable (mean change negative 2.0 plus or minus 10.54 grams per square meter at month 30), whereas in the placebo arm it increased by 5.6 plus or minus 8.26 grams per square meter [17]. Left ventricular ejection fraction improved by 4.6 plus or minus 13.32 percentage points with acoramidis and declined by 8.2 plus or minus 7.73 percentage points with placebo [17]. Left ventricular stroke volume increased by a median of 6.5 milliliters per square meter with acoramidis and decreased by 3.0 milliliters per square meter with placebo [17]. Global longitudinal strain remained stable with acoramidis (change of 0.1 plus or minus 2.25 percent) and deteriorated with placebo (change of 2.2 plus or minus 2.78 percent) [17].

Right ventricular ejection fraction improved by 1.8 plus or minus 11.73 percent with acoramidis and declined by 9.6 plus or minus 9.94 percent with placebo [17]. Amyloid regression (defined by T1-mapping criteria) was observed in 3 of 24 acoramidis recipients (12.5 percent) and in none of the placebo recipients [17]. Extracellular volume fraction increased similarly in both groups, suggesting that the structural benefits reflect stabilization of new amyloid deposition rather than clearance of existing deposits [17].

7.7 Ongoing clinical programs

ATTRibute-PN (NCT04882735) is evaluating acoramidis in transthyretin amyloid polyneuropathy [10]. ACT-EARLY (NCT06563895) is a prevention trial in asymptomatic carriers of pathogenic TTR variants [10]. ACT-EARLY OLE (NCT07116473) evaluates long-term safety and tolerability in newly diagnosed ATTR-CM [10]. A real-world evidence study (NCT07306949) is assessing clinical efficacy of acoramidis in association with cardiac biomarkers [10].

8. Sourcing and Quality Verification

Pharmaceutical-grade acoramidis is available as the marketed product Attruby (712 milligram oral tablets containing acoramidis free acid) in the United States and as Beyonttra in the European Union. The marketed formulation is the highest-quality source for research applications requiring regulatory-grade material.

Research-grade acoramidis (as the free acid or hydrochloride salt) is available from multiple chemical suppliers (MedChemExpress, Selleckchem, Cayman Chemical, TargetMol, BenchChem, and others) at purity greater than 98 percent by high-performance liquid chromatography. Supply is typically in milligram to gram quantities; pricing varies by quantity and supplier.

Investigators should confirm compound identity and purity on every research-grade lot through:

High-performance liquid chromatography area-percent purity determination, with a target of greater than 98 percent.

Mass spectrometry confirmation of molecular weight (expected protonated molecular ion $[M + H]^+$ at mass-to-charge ratio 293.12 for the free acid).

Proton nuclear magnetic resonance spectroscopy to confirm the presence of the dimethylpyrazole, propyloxy linker, and fluorobenzoic acid moieties and the absence of synthesis-related impurities.

Fluorine-19 nuclear magnetic resonance spectroscopy as an orthogonal confirmation of the single fluorine environment.

Karl Fischer titration or loss-on-drying analysis for residual water content.

The absence of a chiral center simplifies identity verification relative to stereoselective compounds. The primary analytical concern is confirmation that the material is the intended free acid or hydrochloride salt (the two forms have distinct molecular weights and solubility profiles) and that UGT-susceptible impurities or degradation products are absent.

9. Reconstitution and Handling

Acoramidis free acid is a white to off-white crystalline powder with moderate aqueous solubility in the free acid form and enhanced solubility as the hydrochloride salt. For research applications:

Stock solutions for in vitro assays are typically prepared at 10 to 100 millimolar in dimethyl sulfoxide (DMSO) and stored at negative 20 degrees Celsius in sealed amber glass vials or in inert-atmosphere sealed tubes. Aqueous working dilutions should be prepared fresh from DMSO stocks immediately before use; the compound's carboxylic acid group may undergo pH-dependent ionization affecting solubility at acidic pH.

For cell-based assays, the final DMSO concentration should be maintained below 0.1 percent (volume per volume) to avoid solvent-mediated cytotoxicity. Working concentrations in the range of 1 to 100 micromolar are typical for TTR stabilization assays.

The solid compound should be stored at room temperature in a dry environment protected from light. Stability of the solid at room temperature is excellent; the marketed formulation does not require refrigeration. Solutions in DMSO are stable for at least 6 months at negative 20 degrees Celsius. Repeated freeze-thaw cycles of DMSO stocks should be minimized; aliquoting into single-use volumes is recommended.

For animal dosing, the compound can be formulated in standard oral vehicles (methylcellulose, hydroxypropyl methylcellulose, polyethylene glycol 400) at concentrations of 1 to 50 milligrams per milliliter. Oral bioavailability has been confirmed in rodent and canine species [1, 5].

10. Stack Interaction Considerations

Acoramidis interacts with several compound classes through its UGT-mediated metabolism, its transporter substrate and inhibitor properties, and its TTR-binding pharmacodynamics. Investigators using acoramidis in combination research or in subjects receiving concomitant medications should consider:

UGT inducers: Compounds that induce UGT enzymes (rifampin, phenobarbital, phenytoin, carbamazepine) may decrease acoramidis plasma exposure through enhanced glucuronidation. Coadministration may require dose adjustment or pharmacokinetic monitoring to maintain adequate TTR stabilization [2].

CYP2C9 substrates: Acoramidis may increase plasma concentrations of CYP2C9 substrates. Warfarin, the most clinically significant CYP2C9 substrate, should be monitored closely if coadministered; INR monitoring with dose adjustment is prudent. Other CYP2C9 substrates of concern include phenytoin, celecoxib, and losartan [2].

Other TTR stabilizers: Concomitant use with tafamidis is pharmacologically plausible (both agents bind the T4 pocket) but has not been studied in formal drug-drug interaction trials. In the ATTRIBUTE-CM trial, approximately 10 percent of patients had prior tafamidis exposure, and a post-hoc analysis indicated that acoramidis efficacy was unaffected by concomitant tafamidis use [15]. However, the clinical rationale for dual TTR stabilizer therapy is unclear, as a single high-potency stabilizer should achieve near-complete target engagement.

TTR gene silencers: Combination of acoramidis with siRNA agents (patisiran, vutrisiran) or antisense oligonucleotides (inotersen, eplontersen) that reduce TTR production represents a mechanistically complementary approach (stabilize remaining TTR plus reduce total TTR burden). This combination has not been prospectively evaluated but is of substantial research interest. In the HELIOS-B trial, approximately 40 percent of participants in the overall population received background tafamidis, suggesting that stabilizer plus silencer combinations are entering clinical practice [12].

Diuretics and heart failure medications: Acoramidis does not have characterized pharmacokinetic interactions with loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or mineralocorticoid receptor antagonists. The ATTRIBUTE-CM trial permitted standard heart failure therapy as background medication [9].

OAT substrates: Although acoramidis inhibits OAT1 and OAT3 in vitro, clinical studies demonstrated no significant interaction with adefovir (OAT1 substrate) or oseltamivir carboxylate (OAT3 substrate) [2]. No dose adjustment of concomitant OAT substrates is required at the approved dose.

Uricosuric considerations: The elevated incidence of gout in the acoramidis arm of ATTRIBUTE-CM (10.9 versus 8.1 percent) raises the possibility of an effect on renal uric acid handling, potentially related to the OAT transporter interactions [9, 15]. Investigators should monitor uric acid levels in research participants, particularly those with pre-existing hyperuricemia.

11. Adverse Events and Safety

11.1 Phase 1 safety in healthy volunteers

In the Phase 1 study of 56 healthy adults, AG10 was uniformly well tolerated across all dose levels (50 to 800 milligrams single dose; 100 to 800 milligrams twice daily for 12 days) [3]. No dose-limiting toxicities, deaths, or serious adverse events were reported. No clinically important changes in safety laboratory tests, vital signs, or electrocardiographic parameters were observed [3]. The adverse event profile was comparable to placebo.

11.2 Phase 3 ATTRibute-CM safety

In the 30-month Phase 3 trial, overall adverse event incidence was similar between acoramidis and placebo (98.1 percent versus 97.6 percent) [9, 15]. Serious adverse events were numerically less frequent in the acoramidis arm (54.6 percent) than the placebo arm (64.9 percent), reflecting the disease-modifying benefit of treatment in a progressive, lethal disease [15].

Adverse events occurring at higher frequency with acoramidis than placebo included:

Diarrhea: 11.6 percent versus 7.6 percent [11, 15].

Upper abdominal pain: 5.5 percent versus 1.4 percent [11, 15].

Gout: 10.9 percent versus 8.1 percent (non-serious); 0.24 percent versus 0 percent (serious) [15].

These gastrointestinal events were generally mild in severity [11]. The gout signal may reflect renal transporter-mediated effects on uric acid handling. No clinically important hepatic, hematologic, renal, or cardiac safety signals were identified that differentiated acoramidis from placebo [9].

11.3 Long-term safety

In the open-label extension through 42 months of treatment, no new clinically important safety issues were identified [16]. The adverse event profile remained consistent with the 30-month data from the randomized period. Long-term real-world safety data are accumulating following the November 2024 approval.

11.4 Special population considerations

Data on use in pregnancy, lactation, and pediatric populations are not available from the clinical development program [2]. The compound is approved for adult use only. No dose adjustment is required for renal impairment [2, 3]. The majority of Phase 3 participants were male (approximately 90 percent) and elderly (mean age approximately 77 years), reflecting the demographics of ATTR-CM; the safety profile in younger patients and in women is less well characterized [9].

12. Comparative Assessment

This section presents a structured comparison of five transthyretin-directed therapies against acoramidis, scored on five competency standards: novelty (mechanism distinctiveness), effect size (magnitude of clinical benefit), promising potential (current developmental trajectory), side-effect profile, and overall validation (quality and maturity of evidence). The five comparators span the two principal mechanistic classes in ATTR-CM: TTR stabilizers (which prevent tetramer dissociation) and TTR gene silencers (which reduce hepatic TTR production).

12.1 Tafamidis (Vyndaqel/Vyndamax)

Mechanism: Selective TTR kinetic stabilizer (benzoxazole derivative). Binds the thyroxine binding sites of the TTR tetramer with a K_d of 4.4 nanomolar by ITC, comparable to acoramidis, but with predominantly entropy-driven binding thermodynamics (ΔH negative 5.0 kilocalories per mole) rather than enthalpy-driven [5]. Reaches peak plasma concentration within 4 hours and has a long elimination half-life of approximately 59 hours, permitting once-daily dosing [11].

Development trajectory: Developed by FoldRx Pharmaceuticals (acquired by Pfizer in 2014). First approved in Europe in 2011 for transthyretin familial amyloid polyneuropathy, then approved by the FDA in May 2019 for ATTR-CM following the ATTR-ACT trial [11, 12]. The ATTR-ACT trial randomized 441 patients to tafamidis 80 milligrams, tafamidis 20 milligrams, or placebo for 30 months and demonstrated a win ratio of 1.695 (95 percent confidence interval 1.255 to 2.289; P less than 0.001), a 30 percent reduction in all-cause mortality (29.5 percent versus 42.9 percent; hazard ratio 0.70, 95 percent confidence interval 0.51 to 0.96), and a 32 percent reduction in cardiovascular hospitalization rates [11, 18].

Clinical outcome: Tafamidis is the most widely prescribed TTR stabilizer globally, with extensive real-world evidence from the THAOS registry showing 84.4 percent survival at 30 months and 76.8 percent at 42 months in treated patients, versus 70.0 percent and 59.3 percent in untreated patients [14]. It is the established standard of care for ATTR-CM.

Novelty: 3/5. First-in-class TTR stabilizer for cardiac amyloidosis; the mechanism was novel at introduction but is no longer unique.

Effect size: 4/5. Large clinical trial with significant mortality and hospitalization reductions. The network meta-analysis by Aimo et al. (2025) ranked tafamidis first (SUCRA 82 percent) for the composite of all-cause mortality and cardiovascular hospitalization [19]. Six-minute walk distance difference from placebo was 59 meters, and KCCQ-OS difference was 11 points [19].

Promising potential: 5/5. Established standard of care with long-term safety data, broad regulatory approval, and extensive real-world evidence.

Side-effect profile: 5/5. Adverse event profile in ATTR-ACT was similar to placebo. No clinically important safety signals in more than five years of real-world experience [14, 18].

Overall validation: 5/5. Highest level of evidence maturity among TTR-directed therapies.

Comparison to acoramidis: In head-to-head biochemical assays, acoramidis demonstrates greater TTR stabilization than tafamidis in serum-based and FPE assays (95.4 versus 41.5 percent at clinical concentrations), attributed to its enthalpy-driven binding and lower albumin competition [5]. However, in the subunit exchange gold-standard assay, the two compounds show similar potency at therapeutic concentrations [14]. Clinically, the ATTRIBUTE-CM composite hazard ratio (0.64) is numerically more favorable than ATTR-ACT (0.70), but cross-trial comparison is limited by differences in baseline disease severity and era of treatment [14, 19]. Acoramidis requires twice-daily dosing versus once-daily for tafamidis.

12.2 Diflunisal

Mechanism: Nonsteroidal anti-inflammatory drug (NSAID) that stabilizes the TTR tetramer at the T4 binding site. Binding affinity is substantially lower than acoramidis or tafamidis (K_d 407 nanomolar by ITC) [5]. At the clinical dose of 250 milligrams twice daily, plasma concentrations of 100 to 200 micromolar provide moderate TTR stabilization [14].

Development trajectory: Diflunisal was developed as an analgesic and anti-inflammatory agent and was never specifically developed for ATTR amyloidosis. Its TTR-stabilizing properties were recognized by the Kelly laboratory at Scripps

Research Institute. A randomized, double-blind, placebo-controlled trial in 130 patients with hereditary ATTR polyneuropathy (Berk et al. 2013) demonstrated reduced neurological progression over two years [12]. It has been used off-label for ATTR-CM on the basis of retrospective analyses showing improved cardiac parameters [12].

Clinical outcome: Not approved for any ATTR indication. Retrospective data in 81 ATTR-CM patients showed measurable cardiac improvements at one year [12]. The compound is now largely supplanted by tafamidis and acoramidis.

Novelty: 2/5. Repurposed NSAID, not designed for TTR stabilization.

Effect size: 2/5. Evidence limited to retrospective analyses in ATTR-CM; no randomized cardiac outcomes trial.

Promising potential: 1/5. Used as a last resort when other stabilizers are unavailable; active development has ceased.

Side-effect profile: 2/5. Significant safety concerns: gastrointestinal bleeding, renal dysfunction, fluid retention, worsening heart failure. Contraindicated when estimated glomerular filtration rate is below 45 milliliters per minute per 1.73 square meters. Requires coadministration with gastroprotection [12].

Overall validation: 2/5. Low-quality evidence (retrospective, observational) and substantial safety concerns.

Comparison to acoramidis: Diflunisal is approximately 85-fold less potent than acoramidis at the TTR binding site [5] and achieves lower TTR stabilization at clinical concentrations. The NSAID-related toxicity profile makes long-term use hazardous in the elderly heart failure population typical of ATTR-CM. Acoramidis supersedes diflunisal on every competency standard.

12.3 Patisiran (Onpattro)

Mechanism: Small interfering RNA (siRNA) agent encapsulated in a lipid nanoparticle, targeting the 3-prime untranslated region of TTR messenger RNA in hepatocytes. Reduces hepatic TTR production by approximately 80 percent, thereby lowering the substrate available for amyloid formation [12, 20].

Development trajectory: Developed by Alnylam Pharmaceuticals. Approved by the FDA in 2018 for hereditary ATTR polyneuropathy (APOLLO trial). The APOLLO-B trial (360 patients, Phase 3) evaluated patisiran 0.3 milligrams per kilogram intravenously every three weeks for ATTR-CM [12]. The trial demonstrated less decline in six-minute walk distance and higher KCCQ-OS scores versus placebo, but all-cause mortality and cardiovascular hospitalizations did not differ between groups [12]. The FDA denied the supplemental application for the ATTR-CM indication, citing "insufficient evidence of clinically meaningful benefit" [11].

Novelty: 5/5. Gene silencing mechanism is fundamentally distinct from TTR stabilization.

Effect size: 2/5. Functional capacity and quality of life preserved, but no mortality or hospitalization benefit demonstrated in ATTR-CM [12, 19].

Promising potential: 2/5. ATTR-CM indication denied by FDA. The compound remains available for hereditary ATTR polyneuropathy.

Side-effect profile: 3/5. Infusion-related reactions, arthralgia, muscle spasms. Requires premedication (corticosteroid, acetaminophen, antihistamines) [12]. Intravenous administration every three weeks is less convenient than oral dosing.

Overall validation: 3/5. Strong evidence in polyneuropathy; weak evidence in cardiomyopathy.

Comparison to acoramidis: The gene silencing mechanism is complementary to TTR stabilization and addresses the amyloidogenic process upstream. However, the failure to demonstrate mortality or hospitalization benefit in ATTR-CM positions patisiran behind acoramidis for the cardiac indication. The combination (stabilizer plus silencer) is of research interest but unvalidated.

12.4 Vutrisiran (Amvuttra)

Mechanism: siRNA agent with N-acetylgalactosamine (GalNAc) conjugate delivery system, targeting TTR messenger RNA in hepatocytes. Subcutaneous administration every 12 weeks. More potent and longer-acting than patisiran, with a distinct delivery mechanism that avoids lipid nanoparticle-related infusion reactions [12].

Development trajectory: Developed by Alnylam Pharmaceuticals. Approved by the FDA in June 2022 for hereditary ATTR polyneuropathy. The HELIOS-B trial (655 patients, Phase 3) evaluated vutrisiran 25 milligrams subcutaneously every 12 weeks for 36 months in ATTR-CM [12]. The overall population (including patients on background tafamidis) showed a 28 percent reduction in the composite of all-cause mortality and recurrent cardiovascular events (hazard ratio 0.72, 95 percent confidence interval 0.56 to 0.93; P equals 0.01) [12]. In the monotherapy subgroup (patients not on background tafamidis), the hazard ratio was 0.74 (95 percent confidence interval 0.58 to 0.91) [19].

Novelty: 4/5. GalNAc-conjugated siRNA mechanism is a significant advance over lipid nanoparticle delivery, with subcutaneous quarterly dosing.

Effect size: 4/5. Significant reduction in mortality and cardiovascular events demonstrated in a large Phase 3 trial. Six-minute walk distance difference from placebo of 32 meters (monotherapy) and KCCQ-OS difference of 9 points [19].

Promising potential: 5/5. Active regulatory pathway for ATTR-CM indication. Quarterly subcutaneous dosing has strong patient convenience advantages.

Side-effect profile: 4/5. Well tolerated, with the majority of adverse events categorized as mild or moderate. No premedication required (unlike patisiran) [12].

Overall validation: 4/5. Large Phase 3 trial with positive mortality and cardiovascular event endpoints; regulatory approval for ATTR-CM pending.

Comparison to acoramidis: Vutrisiran addresses the amyloidogenic cascade at a different node (TTR production rather than TTR stability) and therefore represents a complementary rather than directly competing approach. In the network meta-analysis, the point estimates for vutrisiran monotherapy and acoramidis are similar for the composite endpoint (hazard ratios 0.74 and 0.76, respectively) [19]. Acoramidis has the advantage of oral administration and an approved ATTR-CM indication; vutrisiran has the advantage of quarterly dosing and the potential for combination with a stabilizer.

12.5 Eplontersen (Wainua)

Mechanism: Antisense oligonucleotide (ASO) targeting TTR messenger RNA. Ligand-conjugated ASO (GalNAc) with subcutaneous administration. Reduces serum TTR by approximately 70 percent [12].

Development trajectory: Developed by Ionis Pharmaceuticals in collaboration with AstraZeneca. Approved by the FDA in December 2023 for hereditary ATTR polyneuropathy (NEURO-TTRansform trial). The CARDIO-TTRansform trial (NCT04136171) is a Phase 3 trial enrolling approximately 1,438 patients with ATTR-CM, with results expected in 2025 [12]. Dosing is 45 milligrams subcutaneously every four weeks [12].

Novelty: 3/5. ASO mechanism is established; GalNAc conjugation improves hepatic targeting and safety over first-generation ASOs such as inotersen.

Effect size: Not yet determined for ATTR-CM. NEURO-TTRansform demonstrated a 70.4 percent reduction in serum TTR and significant improvement in neuropathy endpoints [12].

Promising potential: 4/5. Large Phase 3 cardiac trial ongoing; positive polyneuropathy data; monthly subcutaneous dosing.

Side-effect profile: 4/5. Substantially improved safety compared to inotersen (which caused glomerulonephritis and thrombocytopenia). Well tolerated in polyneuropathy trials [12].

Overall validation: 3/5. Validated in polyneuropathy; ATTR-CM data pending.

Comparison to acoramidis: Eplontersen is a gene silencer (like patisiran and vutrisiran) and therefore mechanistically complementary to acoramidis. The ATTR-CM efficacy data are not yet available. If CARDIO-TTRansform is positive, eplontersen would represent a monthly subcutaneous alternative to quarterly vutrisiran and to daily oral acoramidis. The combination of acoramidis plus eplontersen is of research interest as a dual-mechanism approach.

12.6 Comparator summary

The five comparators occupy distinct positions in the ATTR-CM therapeutic landscape. **Tafamidis** is the established standard of care with the deepest evidence base, the longest real-world track record, and the most favorable convenience profile (once daily, oral). **Diflunisal** is a low-potency alternative with substantial safety limitations, used only when other agents are unavailable. **Patisiran** demonstrated gene silencing efficacy in polyneuropathy but failed to achieve clinical endpoints in

ATTR-CM. **Vutrisiran** is the most promising gene silencer for ATTR-CM, with quarterly dosing and a positive Phase 3 trial. **Eplontersen** has a large cardiac outcomes trial pending and represents the monthly subcutaneous option.

Acoramidis occupies a position defined by: (1) the highest TTR stabilization potency in serum-based assays among the stabilizers, attributed to its enthalpy-driven T119M-mimetic binding mechanism; (2) a positive Phase 3 trial with significant reductions in cardiovascular hospitalization and a favorable trend in mortality; (3) an emerging evidence base for cardiac structural benefits (CMR substudy); (4) a manageable adverse event profile comparable to placebo; and (5) twice-daily oral dosing. The principal open questions are whether the biochemical potency advantage over tafamidis translates to clinically meaningful superiority (cross-trial comparisons suggest similar magnitude of benefit but are not definitive), and whether TTR stabilization alone or in combination with gene silencing will prove optimal for long-term disease modification in ATTR-CM.

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