

Supplementary Table 1: Summary of Clinical Trials for Novel Therapeutic Agents in ATTR-CM

Agent	Clinical Trial	Year	Study Design	Follow-up Period	Population	Outcomes
TTR Stabilizers						
Tafamidis ¹	ATTR-ACT	2018	Phase III Multicenter Double-blind Placebo-controlled Randomized 2:1:2 (80 mg daily : 20 mg daily : placebo)	30 months	441 patients with ATTRv-CM or ATTRwt-CM	Primary: Tafamidis was superior to placebo via hierarchal assessment of all-cause mortality followed by frequency of cardiovascular (CV)-related hospitalizations after 30 months (Win ratio 1.695 (95% CI 1.255–2.289) Lower all-cause mortality (HR 0.70; 95% CI 0.51–0.96) Lower CV hospitalizations (RR 0.68; CI 0.56–0.81) Secondary: Tafamidis had greater 6-minute walk distances (6MWD) (p<0.001) and lower rate of decline in KCCQ-OS scores (p<0.001).
Acoramidis ²	ATTRibute-CM	2024	Phase III Multicenter Double-blind Placebo-controlled Randomized 2:1 (acoramidis 800 mg twice daily vs placebo)	30 months	632 patients with ATTRv-CM or ATTRwt-CM and symptomatic heart failure	Primary: Hierarchical analysis including all-cause mortality, CV hospitalizations, change in NT-probing levels and 6MWD favored acetamidis over placebo (Win ratio 1.8 [95% CI 1.4–2.2], Finkelstein-Schoenfeld test statistic 5.015, p<0.001) Secondary: Compared to placebo, acoramidis had smaller decline in 6MWD (39.6 m; 95% CI 21.2–58.2), KCCQ-OS (least squares mean difference 9.94 points; 95% CI 5.92-13.91; p<0.001), and higher serum TTR (7.01 mg/dL; 95% CI 5.79-8.40; p<0.001) at 30 months.
TTR Silencers						
Revusiran ³	ENDEAVOUR	2020	Phase III Multicenter Randomized Double-blind Placebo-controlled	Stopped at median 6.71 months	206 patients with ATTRv-CM	Trial discontinued due to higher mortality with revusiran (12.9%) vs placebo (3.0%) (HR 5.3; 95% CI 1.2–22.8).
Patisiran ⁴	APOLLO-B	2023	Phase III multicenter randomized double-blind placebo-controlled Randomized 1:1 for patisiran 0.3 mg/kg intravenously every 3 weeks for 12 months (max dose 30mg or placebo)	12 months	360 patients with ATTR amyloidosis and cardiomyopathy Patisiran n=181 Placebo n=179	Primary: Preserved functional capacity in patisiran group compared to placebo(p=0.02). Secondary: Compared with placebo, patisiran had smaller decline in KCCQ-OS (p=0.04), smaller NT-proBNP increase (p<0.05), and all-cause mortality/CV events/change in 6MWD (Win ratio 1.27 (95% CI 0.99–1.61)).

Vutrisiran ⁵	HELIOS-B	2024	Phase III Global/Multicenter Randomized Double-blind, Placebo-controlled Randomized 1:1 to receive subcutaneous vutrisiran (25 mg) or placebo every 12 weeks	Up to 36 months	655 patients with ATTR-CM Vutrisiran n=326 Placebo n=329	Primary: Vutrisiran group had reduced risk of all-cause death and recurrent CV events (overall population HR 0.72; 95% CI 0.56-0.93; p=0.01; monotherapy HR 0.67; 95% CI 0.49-0.93; p=0.02). Secondary: Vutrisiran group had lower risk death from any cause through 42 months compared to placebo (HR in overall population 0.65; CI 0.46-0.90; p=0.01; HR in monotherapy 0.66; CI 0.44 – 0.97; p=0.045). Compared to placebo, vutrisiran had smaller decline in 6MWD (26.5 m) and KCCQ-OS (5.8 points; both p<0.001).
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Eplontersen ⁶	CARDIO-TTRansform	2020– current	Phase III Multicenter Randomized Double-blind Placebo-controlled Randomized 2:1 to receive subcutaneous injections every 4 weeks of eplontersen (45 mg) or placebo with vitamin A supplementation	140 weeks	1,438 patients with ATTR-CM Eplontersen n=959 Placebo n=479	<i>Ongoing</i> Primary: Composite CV mortality and recurrent CV events up to 140 weeks. Secondary: Change in 6MWD and KCCQ-OS at 121 weeks from baseline
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NTLA-2001 ⁷	MAGNITUDE	2024– current	Phase III Multicenter Randomized Quadruple-blind Placebo-controlled Randomized 2:1 for single intravenous infusion (55 mg) or placebo	18 months to 4 years	765 patients with ATTRv-CM or ATTRwt-CM NTLA-2001 n=510 Placebo n=255	<i>Ongoing</i> Evaluating the efficacy and safety of a single-dose CRISPR-Cas9 therapy targeting the TTR gene Primary: Composite CV mortality and CV event frequency. Secondary: Change in TTR concentration and KCCQ-OS from baseline
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TTR Fibril Depleting Agents

ALXN2220 ⁸	DepleTTR-CM	2024– current	Phase III Randomized Quadruple-blind Placebo-controlled Randomized to receive 0.3 mg/kg or placebo intravenously every 4 weeks for at least 24 months, up to 48 months maximum	24–48 months	~1,000 patients with ATTRv-CM or ATTRwt-CM	<i>Ongoing</i> Evaluate safety and efficacy of a monoclonal antibody against TTR fibrils in myocardium of ATTR-CM patients Primary: Total CV mortality and CV events at 48 months Secondary: Change from baseline in KCCQ-OS and 6MWD at 24 months; time to all-cause mortality up to 48 months
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Coramitug ⁹	—	2018– current	Phase II Global Randomized Quadruple-blind Placebo-controlled Randomized for intravenous infusion (2 different doses or placebo) every 4 weeks added to standard of card until week 52	64 weeks	99 patients with ATTRv-CM or ATTRwt-CM Coramitug n=66 Placebo n=33	<i>Ongoing</i> Primary: Change in 6MWD and NT-proBNP at 52 weeks Secondary: Change in ECV, KCCQ, NIS, troponin I, GLS, CV events at 52 weeks
AT-02 (Attralus) ¹⁰	—	2023– current	Phase II Randomized Double-blind Placebo-controlled Intravenous infusion every 2 or 4 weeks for 104 weeks total	Up to 120 weeks	Up to 100 patients with cardiac AL or ATTR-CM	<i>Ongoing</i> Primary: Safety and tolerability of AT-02 and incidence, frequency, and severity of TEAEs. Secondary: PK parameters (C _{max} , T _{max} , AUC _{last} , AUC _{inf} , V _{ss} , total body clearance, half-life), incidence of anti-drug antibodies, change in baseline biomarkers (NT-proBNP, hsTnT, UACR), serial CMR findings

ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = variant/hereditary transthyretin amyloid disease; ATTRwt = wild type transthyretin amyloid disease; AL = amyloid light chain, AUC_{inf} = area under plasma concentration-time curve extrapolated to infinity, represents total drug exposure; AUC_{last} = area under plasma concentration-time curve from time 0 to last measurable plasma concentration; C_{max} = peak serum concentration; CI = confidence interval; CMR = cardiac MRI; CV = cardiovascular; ECV: extracellular volume HR = hazard ratio; hsTnT = high sensitivity troponin; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; NIS = neuropathy impairment score; PK = pharmacokinetics; PN = polyneuropathy; T_{max} = time it takes drug to reach maximum concentration; TTR = transthyretin; TEAE = treatment emergent adverse event; V_{ss} = steady state volume of distribution; WT = wild type; 6MWD = 6-minute walk distance

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