Drug	Mechanism	Study	Intervention	Inclusion criteria	Outcome	Side effects
Diflunisal	TTR tetramer stabiliser (NSAID)	NCT00294671 Phase 3 Double-blinded Placebo-controlled RCT N=130 1:1 allocation	250mg bd PO for 24 months (with PPI)	- 18-75y.o. - ATTRv-PN - Biopsy proven amyloidosis - Signs of PN or AN - ECOG <3 - NYHA<4	1°: 29.7% diflunisal vs. 9.4% placebo showed reduced rate of neurologic progression (NIS+7) and improved QOL (SF-36) over 2 years	Upper GIT ulceration and GORD Renal impairment Platelet aggregation inhibition and bleeding Hypertension Fluid retention Monitor FBC and EUC 3/12 PPI cover
Tafamidis (Vyndagel; Vyndamax)	TTR tetramer stabiliser	Fx-005 Phase 2/3 Double-blinded Placebo-controlled RCT NCT00409175 N= 128 OLE– 30 months NCT00791492 N= 86	20mg PO daily for 18 months	- 18-75y.o. - ATTRV30M - PN - Biopsy confirmed - KPS >50% (Findings subsequently confirmed in non-V30M mutations)	Fx-005 - No difference in NIS-LL or NF-Qol-DN responder on IIT - EE cohort:60% NIS-LL responders vs 38% placebo; improved NF-Qol_DN OLE - Stabilisation of NIS-LL and NF-QoL-DN - Rate of change of NIS-LL reduced in patients switching from placebo Tafamidis 30/12 56% greater preservation of NIS-LL than late initiation	No difference in AE between Tafamidis and placebo No monitoring required
		ATTR-ACT NCT01994889 Phase 3, Double-blinded, Placebo-controlled RCT N=441 2:1:2 allocation (80mg: 20mg: placebo)	Tafamidis meglumine/ Vyndagel: 80mg daily or 20mg daily PO for 30 months Note: Tafamidis (free acid form)/ Vyndamax 61mg PO daily	- 18-90 y.o. - ATTR-CM (v and wt) - HF symptoms or prior hospitalisation - IVSd >12mm - Biopsy or scintigraphy proven ATTR amyloidosis	1°: Tafamidis showed lower all-cause mortality vs placebo 29.5% vs 42.9% 2°: Cardiovascular-related hospitalisations were reduced RR of 0.68 (0.48 per year vs. 0.70 per year). Except in NYHA class III where hospitalisations > placebo Reduced 6-MWT and KCCQ in Tafamidis vs controls NNT -4	
Acoramadis (AG10/ ALXN2060)	TTR tetramer stabiliser	ATTRibute-CM NCT03860935 Phase 3 Double-	800mg PO bd for 30 months	- 18-90 y.o. - ATTR-CM (v and wt) - HF symptoms or prior hospitalisation - Stable NYHA I-III	Estimated completion May 2023 1°: 6MWT at M12, Composite all-cause	No known SE or interactions

		blinded Placebo controlled RCT N = 632 2:1 allocation		- >150m 6MWT - IVSd >12mm - Biopsy or scintigraphy	mortality, and CV hospitalisations at 30mo 2°: KCCQ M12 and M30, 6MWT M30, All-cause and CV mortality and CV hospitalisation. Phase 2- N 49: near-complete stabilisation of TTR (>90% at D28) Prelim results M12: no difference in 6MWT	
		ATTRibute-PN NCT04882735 Phase 3 Open-label Single-arm N=100	800mg PO bd for 18 months	- 18-90 y.o. - ATTRv-PN - PND<IIIb - NIS 5-130 - NCS sum score >2 - KPS>60%	Not yet Recruiting 1°: Change from baseline mNIS+7; safety 2°: Change in NFQoL-DN, mBMI, COMPASS-31at M18	
Green Tea Extract (EGCG)	TTR resorption	Case cohort N=25	600mg PO daily for up to 12 months	- ATTRwt - Endomyocardial biopsy positive - Gene testing negative	1°: 12 out of 14 showed a decrease of 5.9% in left ventricular myocardial mass on cMR	Liver function derangement (rare liver failure). Insomnia
Doxycycline and TUDCA	TTR synthesis inhibitor and TTR resorption	Phase 2, Single-centre, Open-label, non-randomised NCT01171859 and NCT01855360 N=40	Doxycycline 100mg PO bd and TUDCA 250mg PO tds for 12 months	- >18 y.o - ATTRwt and ATTRv - Biopsy proven ATTR - Symptomatic organ involvement - ECOG<3 - NYHA<3 - SBP>100mmHg	Stable neuropathy in 46% (n=13 evaluable patients) Stable NTproBNP in 75% (n=24 evaluable patients).	Doxycycline: Photosensitive skin reactions GIT side effects. TUDCA: no significant AE
Inotersen (Tegsedi, IONIS-TTR Rx, ISIS 420915)	ASO	NEURO-TTR NCT01737398 Phase 2/3 Double-blinded, Placebo-controlled RCT N=172 2:1 allocation	300mg SC x 3 in W1, followed by 300mg SC weekly for 16 months (+3000IU Vitamin A OD)	- 18-82 y.o. - ATTRv-PN - biopsy confirmed ATTR - NIS 10-130 - PND <3 - KPS >50 - NYHA<3	1°: Improvement or non-progression in polyneuropathy (mNIS+7) 37% Inotersen vs 19% placebo. Improvement or non-progression in NF-QoL-DN 50% vs 27%	SAE: - Glomerulonephritis 3% - Severe thrombocytopenia (<25,000mm$^{3)}$ 3% including 1 death due to ICH due to grade 4 thrombocytopaenia Mild-Mod AE - Thrombocytopenia (<140,000mm^3) in 54% vs 13% placebo - Infusion/injection reactions Vitamin A Deficiency **Monitor**: EUC, FBC, Urine analysis 2 weekly Supplement Vitamin A
		NCT03702829 Phase 2 Open-label N=50	300mg SC weekly for 24 months (+3000IU Vitamin A OD)	-18-85 y.o - ATTR-CM (v or wt) - either biopsy or DPD positive - stable NYHA I-III	Estimated completion March 2022 1°: LV strain compared with baseline at M6 2°: LV strain compared with baseline at M12, M18, M24, cMR extracellular volume at M6, M12, M24	
Eplontersen	ASO	Neuro-	45mg SC	- 18-82y.o.	Estimated	Vitamin A Deficiency

(AKCEA-TTR-LRx, IONIS-TTR-LRx, ION-682884)	conjugated to GaINAc	TTRansform NCT04136184 Phase 3 Open-label Crossover study RCT N=168	every 4 weeks for 65 weeks (vs Inotersen SC weekly) (+3000IU Vitamin A OD)	- ATTRv-PN - Coutinho 1-2 - NIS 10-130	completion Jan 2024 1°: Change in mNIS+7 and NF-QoL-DN at W66, change in TTR serum concentrations 2°: Change in mNIS+7, NF-QOL-DN at W35, SF-36, PND and mBMI at W65.	Supplement Vitamin A
		Cardio-TTRansform NCT04136171 Phase 3 Double-Blinded Placebo-controlled RCT Ongoing enrolment estimated N= 750	45mg SC every 4 weeks (+3000IU Vitamin A OD)	- 18-90 y.o. - ATTR-CM - Biopsy or Bone scintigraphy confirmed ATTR - NYHA I-III - IVSd >12mm	Estimated completion June 2024 1°: Composite of CV mortality and recurrent CV clinical events at M30 2°: Change in baseline 6MWT, KCCQ, CV mortality, CV events, All-cause mortality at M30	
Patisiran (Onpattro, ALN-TTR02)	siRNA	APOLLO NCT01960348 Phase 3, Double-blinded, Placebo-controlled, RCT N=225 2:1 allocation	0.3mg/kg IVI, 3 weekly (max 30mg) for 18 months (+3000IU Vitamin A OD and infusion premedications – IV steroid, paracetamol, H1- and H2-receptor blockers)	- 18-85 y.o. - ATTRv-PN - NIS: 5-130 - PND <IIIb - NYHA<3	**1°:** Improvement or less progression in polyneuropathy scores (mNIS+7) in 56% vs 4% **2°:** Improvements in NFQoL-DN, 10-MWT, NIS, mBMI, R-ODS and COMPASS31 scores.	SAE: similar between Patisiran and placebo Mild-Mod AE: - Peripheral oedema 20% vs 22% - Infusion-related reactions (19% vs 9%) Vitamin A Deficiency Supplement Vitamin A
		APOLLO-B NCT03997383 Phase 3, Double-blinded, Placebo-controlled, RCT N=360	0.3mg/kg IVI, 3 weekly for 12 months (+3000IU Vitamin A OD and infusion premedications – IV steroid, paracetamol, H1- and H2-receptor blockers)	- 18-85 y.o. - ATTR-CM (v or wt) - HF symptoms or prior hospitalisation - Stable HF (no hospitalisation in 6/52) - Tafamidis naive, or progression on Tafamidis >6/12 - >150m on 6MWT - NTproBNP >300ng/L and <8500ng/L or if AF >600ng/L and <8500ng/L	Estimated completion June 2025. Outcome measures: 1°: Change in 6MWT from baseline to 12 mo 2°: Change in KCCQ score, All-Cause mortality, CV events	
Vutisiran (ALN-TTRSC02)	siRNA conjugated to GaINAc	HELIOS-A NCT03759379 Phase 3, Open-label, RCT N=164 3:1 allocation	25mg SC every 12 weeks (vs Patisiran IV and Placebo cohort from APOLLO) for 18 months (+ 3000 IU Vitamin A daily)	- 18-85 y.o. - ATTRv-PN - NIS 5-130 - PND <IIIb - KPS>60%	Estimated completion May 2024 1°: Change in mNIS+7 at 9 months 2°: Change in NF QoL-DN, 10-MWT at M9, Change in m+NIS, NF QoL-DN, 10-MWT, mBMI,	Mild-Mod AE - Injection site reactions Vitamin A Deficiency Supplement Vit A

					R-ODS at M18 Interim 9/12 reporting: improved mNIS+7, NF QoL-DN, and stability of 10-MWT, NTproBNP c/w Placebo	
		HELIOS-B NCT04153149 Phase 3 Double-blinded, Placebo-controlled RCT N= 665	25mg SC every 12 weeks (+ 3000 IU Vitamin A daily)	- 18-85 y.o. - ATTR-CM (v or wt) - HF symptoms or prior hospitalisation	Estimated completion June 2025 Outcome measures: 1°: Composite outcome of all-cause mortality and recurrent CV hospitalisations at 30-36mo 2°: Change in 6MWT, KCCQ score, LVWT, GLS, mortality, CV events, NTProBNP	
CRISPR-Cas9 gene editing (NTLA-2001)	TTR gene editing	NCT04601051 Phase 1 Open-label, single ascending dose followed by single dose expansion Ongoing recruitment N=74	0.1mg/kg and 0.3mg/kg single dose IV	- 18-80 y.o. - Weight 50-90kg - Lack of access to approved treatments for ATTR ATTRv-PN - No other cause of neuropathy OR ATTR-CM (v or wt) - NYHA I-III - HF symptoms or prior hospitalisation - >150m on 6MWT	Estimated completion Nov 2024 Initial dosing groups n=6: - Durable knock out of TTR after single dose - 0.1mg/kg – 52% and 0.3mg/kg – 87% reduction in TTR concentration at D28	SAE: Nil Mild AE - Infusion reaction - Increased D-dimer
PRX-004 (monoclonal antibody to misfolded TTR)	Amyloid deposit clearance	Phase 1 Open-label Dose-escalation NCT03336580 N=21	IV every 28 days	- >18 y.o. - ATTR biopsy, genetics, scintigraphy proven - KPS>60% - NTproBNP >650 and <5000pg/mL or IVSd >12mm	Terminated due to COVID Dose escalation study to determine safety, tolerability, PK and PD.	TBD
NI006 (monoclonal antibody to misfolded TTR)	Amyloid deposit clearance	Phase 1 Double-blinded, Placebo-controlled Dose-escalation RCT NCT04360434 N=36	IV every 28 days	- >18 y.o. - ATTR-CM (v or wt) - LVEF>40%, LVWT>14mm, NTproBNP >600pg/mL, 6MWT>150m - Stability over 30days - KPS>60%	Estimated completion June 2022 Dose escalation study to determine safety, tolerability, PK and PD.	TBD
Anti-SAP monoclonal antibody (Dezamizumab) and CPHPC (Miridesap)	Deposit elimination	Phase 2 Open-Label Non-randomised NCT03044353 N=7	CPHPC 20mg/hr IV daily for 3 d then anti-SAP antibody D1 and D3 IV, with 60mg CPHPC SC TDS D1-11	- 18-80 y.o. - ATTR-CM (v or wt) – biopsy, genetics or scintigraphy proven - LGE on cMR - LV Mass on cMR> 200g - Stable NYHA 2-3	Study Terminated due to change in benefit/risk profile 1°: Safety and efficacy, change in LV Mass	In Phase 1 (n=23; NCT01777243) self-limiting rash with higher doses

Table 1: Clinical trials in ATTR amyloidosis.

Abbreviations: 6MWT = 6 minute walk test; 10-MWT = 10m walk test; ADL=activities of daily living, AE = adverse events; AN = Autonomic neuropathy; ASO= antisense oligonucleotide, ATTRv= variant (hereditary) transthyretin amyloidosis, bd = bi-daily; cMR = cardiac MRI; COMPASS-31 = Composite Autonomic Symptom Score; CV = cardiovascular; c/w = compared with; D = Day; ECOG = Eastern Cooperative Oncology Group; EUC = Kidney function test; EE = efficacy-evaluatble population; FBC= Full blood count; GaINAc = N-acetyl galactosamine; GIT = Gastrointestinal; GLS = Global longitudinal strain; GORD= gastro-oesophageal reflux disease; HF= Heart failure; IVI=intravenous infusion; IIT = intention to treat; IVSd = Interventricular septal diameter; KCCQ = Kansas City Cardiomyopathy questionnaire; KPS = Karnofsky Performance scale; LGE = Late gadolinium enhancement; LV = Left ventricular; LVEF = left ventricular ejection fraction; LVWT= Left-ventricular wall thickness; M = Month; mBMI = modified BMI; mNIS+7=modified Neuropathy Impairment Scale+7; N = number of participants; NF-QoL-DN= Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NIS-LL= neuropathy Impairment Score lower limb subscale; NNT = number needed to treat; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; OLE = Open-label extension; PD = Pharmacodynamics; PK = Pharmacokinetics; PN = Peripheral neuropathy; PND = polyneuropathy disability score; PO = per-oral; PPI = proton-pump inhibitor; QOL = quality of life; RCT= randomized controlled trial; R-ODS = Rasch-built overall disability scale; RR = relative risk; SAE= serious adverse events, SAP = serum amyloid P; SC = sub-cutaneous, SF-36 = 36-Item Short Form Health Survey; siRNA= small interfering RNA; TBD = To be determined; TDS = Three times daily; W = Week.