Long-Term Effects of Patisiran on Survival and Cardiac Parameters in Patients with Transthyretin-Mediated Cardiac Amyloidosis: Post Hoc Analysis of APOLLO-B and Cardiac Subpopulation of APOLLO OLE

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Background and Rationale

Transthyretin Amyloidosis (ATTR)

- ATTR is a progressive and fatal disease caused by accumulation of toxic TTR amyloid fibrils in multiple organs and tissues, including the heart and nervous system[1–3]
- Ongoing TTR amyloid deposition in the heart drives the progression of cardiomyopathy, leading to worsening heart failure and arrythmias, decline in functional status and quality of life, increased hospitalisations and reduced survival[4–8]
- There are two types of ATTR: hereditary (hATTR) and wild-type (wtATTR)[9]
  - Patients with hATTR commonly develop a mixed phenotype of polyneuropathy and cardiomyopathy, and patients with wtATTR predominantly have cardiomyopathy, although polyneuropathy may coexist[9]

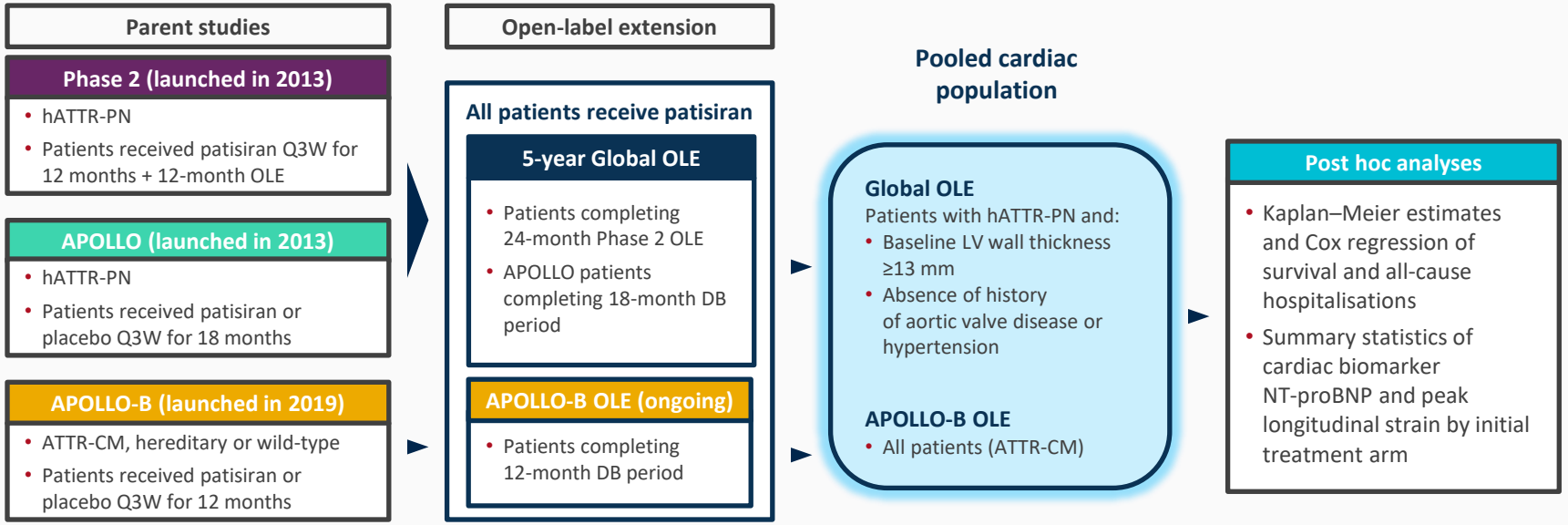
Patisiran Clinical Trials

- Patisiran is an RNAi therapeutic that results in rapid knockdown of serum TTR, as demonstrated in both the APOLLO[10] and APOLLO-B studies[11]
- During clinical development, patisiran was assessed in patients with hATTR-PN, including those with evidence of cardiac involvement in the Phase 2 OLE, Phase 3 APOLLO, and 5-year Global OLE studies, and in patients with ATTR-CM in the Phase 3 APOLLO-B study

Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; hATTR, hereditary ATTR; hATTR-PN, hATTR with polyneuropathy; OLE, open-label extension; RNAi, RNA interference; TTR, transthyretin; wATTR, wild-type ATTR. **References:** 1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 2. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 3. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 4. Castano et al. *Heart Fail Rev* 2015;20:163–78; 5. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 6. Lane et al. *Circulation* 2019;140:16–26; 7. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 8. Gillmore et al. *Eur Heart J* 2018;39:2799–806; 9. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 10. Adams et al. *N Engl J Med* 2018;379:11–21; 11. Maurer et al. *N Engl J Med* 2023;389:1553–65.

Objective and Methods

- To evaluate the long-term benefit of patisiran on survival, hospitalisations and cardiac parameters in a pooled cohort of patients with ATTR and evidence of cardiac involvement or diagnosis of ATTR-CM, across the patisiran clinical trials



Abbreviations: ATTR, transthyretin amyloidosis; DB, double-blind; ATTR-CM, ATTR with cardiomyopathy; hATTR-PN, hereditary ATTR with polyneuropathy; LV, left ventricular; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension; Q3W, every 3 weeks.

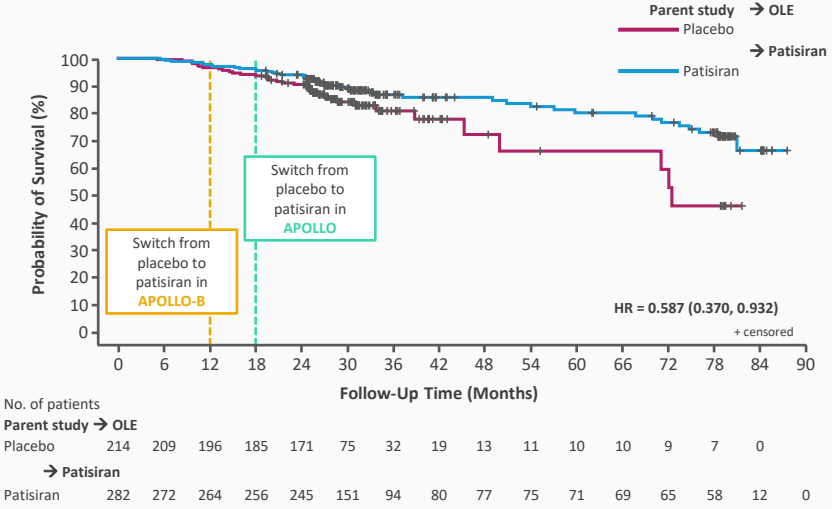
Pooled Cardiac Population Baseline Demographics and Disease Characteristics

Parameter	Patisiran (N=282)				Placebo (N=214)		
	Total (N=282)	APOLLO-B (N=181)	APOLLO (N=90)	Phase 2 (N=11)	Total (N=214)	APOLLO-B (N=178)	APOLLO (N=36)
Age at screening, years, median (range)	**72 (24–85)**	76 (47–85)	60 (24–79)	69 (58–75)	**74 (41–85)**	76 (–85)	62 (43–80)
Male sex, n (%)	**237 (84.0)**	161 (89.0)	68 (75.6)	8 (72.7)	**190 (88.8)**	160 (89.9)	30 (83.3)
Race, n (%)							
White	**212 (75.2)**	138 (76.2)	63 (70.0)	11 (100.0)	**156 (72.9)**	140 (78.7)	16 (44.4)
Asian	**46 (16.3)**	23 (12.7)	23 (25.6)	0	**33 (15.4)**	15 (8.4)	18 (50.0)
Black or African American	**18 (6.4)**	16 (8.8)	2 (2.2)	0	**16 (7.5)**	15 (8.4)	1 (2.8)
Age category, n (%)							
<45	**11 (3.9)**	0	11 (12.2)	0	**3 (1.4)**	2 (1.1)	1 (2.8)
45–<65	**65 (23.0)**	15 (8.3)	48 (53.3)	2 (18.2)	**36 (16.8)**	15 (8.4)	21 (58.3)
65–<75	**94 (33.3)**	61 (33.7)	26 (28.9)	7 (63.6)	**69 (32.2)**	60 (33.7)	9 (25.0)
≥75	**112 (39.7)**	105 (58.0)	5 (5.6)	2 (18.2)	**106 (49.5)**	101 (56.7)	5 (13.9)
wtATTR[a], n (%)	**144 (51.1)**	144 (79.6)	0	0	**144 (67.3)**	144 (80.9)	0
NYHA class[b], n (%)							
Class I	**49 (17.4)**	10 (5.5)	34 (37.8)	5 (45.5)	**31 (14.5)**	15 (8.4)	16 (44.4)
Class II	**218 (77.3)**	156 (86.2)	56 (62.2)	6 (54.5)	**170 (79.4)**	150 (84.3)	20 (55.6)
Class III	**15 (5.3)**	15 (8.3)	0	0	**13 (6.1)**	13 (7.3)	0
NT-proBNP level, ng/L, median (IQR)	**1577 (770–2744)**	2008 (1135–2921)	756 (285–2432)	604 (205–1367)	**1607 (837–2893)**	1813 (952–3079)	846 (373–1582)
Average peak longitudinal strain, %, mean (SEM)	**–12.44 (0.2)**	–10.9 (0.3)	–15.1 (0.4)	–16.6 (1.3)	**–11.96 (0.2)**	–11.2 (0.2)	–15.7 (0.6)

[a]Patients with wtATTR were excluded from the Global OLE studies. [b]Patients with NYHA class ≥III were excluded from the Global OLE studies. **Abbreviations:** IQR, interquartile range; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; SEM, standard error of the mean; wtATTR, wild-type transthyretin amyloidosis.

Impact of Patisiran on Survival and Hospitalisation in the Pooled Cardiac Populations

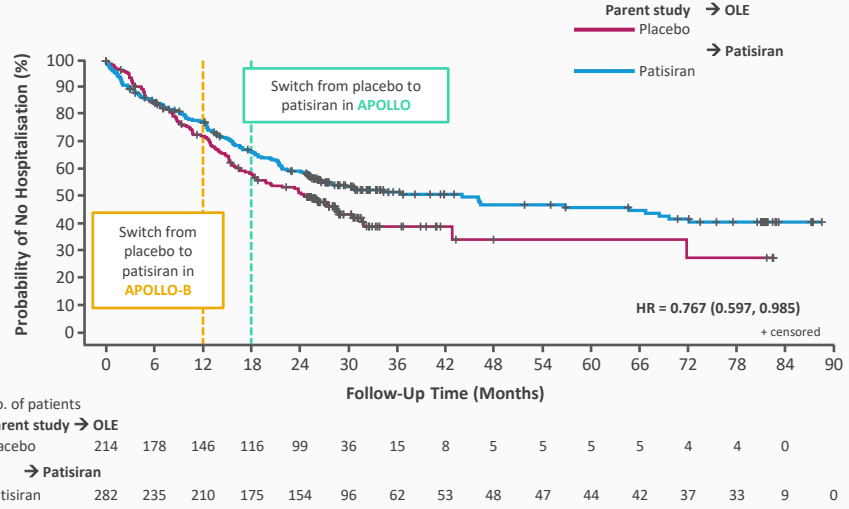
Survival by Initial Treatment Arm



No. of patients

Parent study → OLE															
Placebo	214	209	196	185	171	75	32	19	13	11	10	10	9	7	0
→ Patisiran															
Patisiran	282	272	264	256	245	151	94	80	77	75	71	69	65	58	12	0

Hospitalisations by Initial Treatment Arm



No. of patients

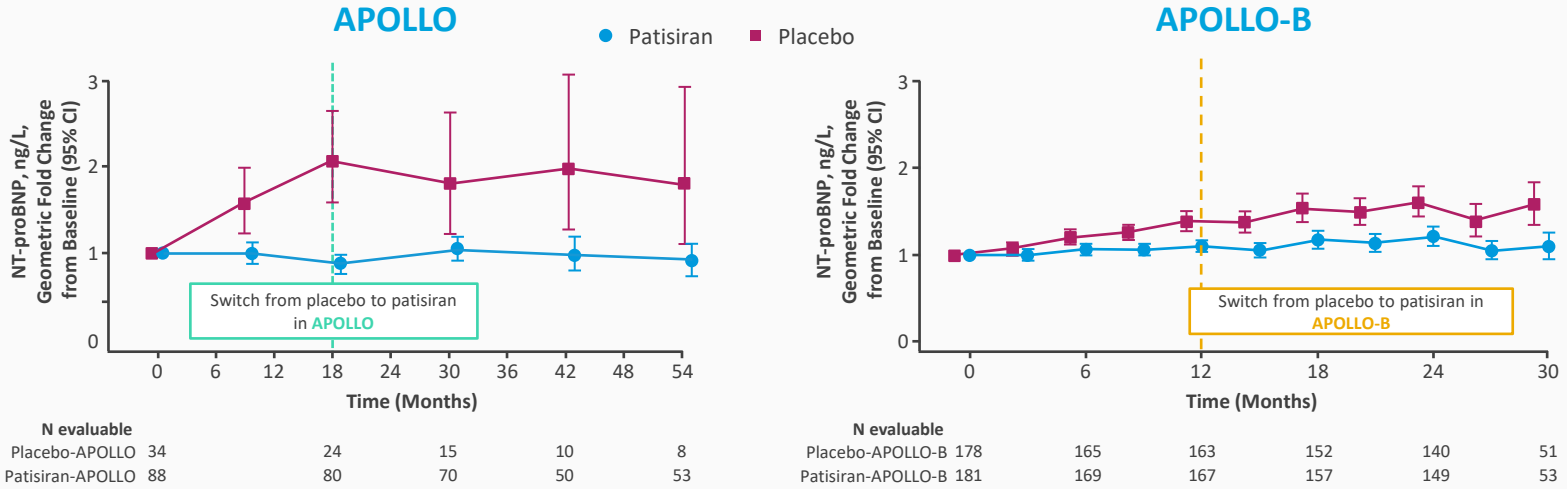
Parent study → OLE															
Placebo	214	178	146	116	99	36	15	8	5	5	5	4	4	0	
→ Patisiran															
Patisiran	282	235	210	175	154	96	62	53	48	47	44	42	37	33	9	0

With early initiation of patisiran treatment in the parent studies:

- The hazard for mortality is decreased by approximately 40%
- The hazard for hospitalisations is decreased by approximately 23%

HR is calculated from a Cox regression model with initial treatment as a covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio; OLE, open-label extension.

Long-Term Stability of NT-proBNP with Patisiran Treatment



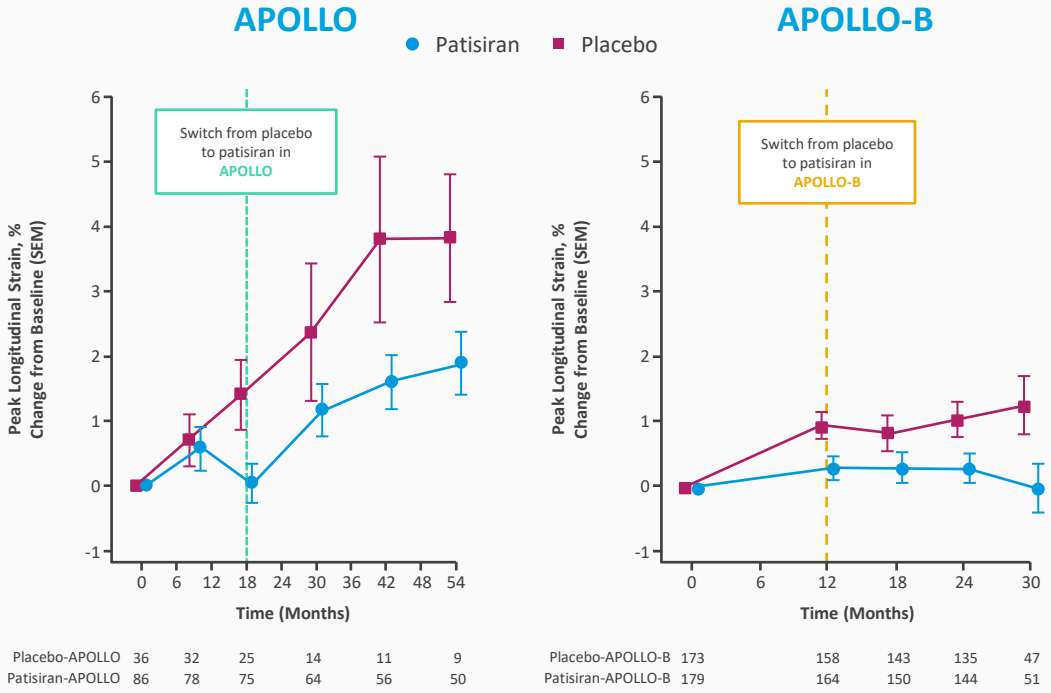
- Patisiran-randomised patients had stable geometric mean fold change in NT-proBNP from baseline throughout APOLLO and APOLLO-B
- The rate of worsening of geometric mean fold change in NT-proBNP from baseline in placebo-randomised patients decreased following the switch to patisiran at Month 18 in APOLLO and at Month 12 in APOLLO-B

Baseline is defined as the baseline of double-blind periods. Geometric mean fold change and 95% CIs obtained by exponentially back-transforming the arithmetic mean and 95% CI of the change from baseline in log-transformed NT-proBNP.

Abbreviations: CI, confidence interval; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide.

Impact of Patisiran on Left Ventricular Function

- Better preservation of peak longitudinal strain among patisiran- compared with placebo-randomised patients in APOLLO and APOLLO-B
- During APOLLO-B:
  - In the patisiran group, peak longitudinal strain remained stable over 30 months
  - In the placebo group, the rate of worsening decreased following the switch to patisiran at Month 12



Baseline is defined as the baseline of double-blind periods.
Abbreviations: SEM, standard error of the mean.

Conclusions

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- Across 4 studies with up to 7 years of follow-up in almost 500 patients with ATTR-CM or evidence of cardiac amyloid involvement, long-term benefits with patisiran were observed for survival, hospitalisations, NT-proBNP and peak longitudinal strain
  - Patisiran-randomised patients had better long-term survival and reduced likelihood of hospitalisation than placebo-randomised patients
  - Patisiran-randomised patients showed relatively stable NT-proBNP and peak longitudinal strain
- Placebo-randomised patients showed reduced rates of worsening in NT-proBNP levels and peak longitudinal strain following the switch to patisiran
- Outcomes were more favourable for those initially randomised to patisiran than placebo, highlighting the beneficial impact of initiating treatment early in the course of disease

Thank you to the patients, their families, Investigators, study staff and collaborators for their participation in the Phase 2, APOLLO and APOLLO-B studies.

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Disclaimer: Patisiran is not indicated for the treatment of ATTR-CM in the USA or EU. ANSM has granted approval for the compassionate use of patisiran in France for patients with ATTR-CM failing tafamidis 61 mg or intolerant to it.

Abbreviations: ANSM, Agence nationale de sécurité du médicament et des produits de santé; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide.