Outpatient Heart Failure Worsening in Patients with Cardiac Transthyretin Amyloidosis: Results from the APOLLO-B Trial

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Conclusions

- **This post hoc analysis assessed the prognostic and clinical significance of outpatient worsening heart failure (HF) characterized by oral diuretic initiation or intensification (ODI) in patients with transthyretin amyloidosis (ATTR) with cardiomyopathy (ATTR-CM)**
- **Overall, patients who experienced an ODI event tended to be at higher risk of all-cause mortality, cardiovascular (CV) hospitalizations, and urgent HF visits**
- **Patisiran treatment significantly reduced worsening HF requiring ODI in the overall population, with consistent results in those receiving and not receiving tafamidis**
- **A significantly greater increase in daily diuretic usage was observed in the placebo group than the patisiran group at Month 12**
- **These data support the potential for outpatient worsening HF as indicated by ODI to be used as an endpoint that responds to ATTR-CM therapy in clinical studies**

Introduction

Transthyretin Amyloidosis (ATTR)

- ATTR is a progressive and fatal disease caused by accumulation of toxic transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including the heart[1–3]
- Ongoing TTR amyloid deposition in the heart drives the progression of cardiomyopathy, leading to worsening HF and arrythmias, decline in functional status and quality of life, increased hospitalizations, and reduced survival[4–8]
- Recent studies have highlighted a prognostic role for ODI as an early and sensitive marker of outpatient HF worsening, with either reduced or preserved ejection fraction[9–12]
- Thus, ODI events may present an early opportunity to recognize progressing disease and intervene

Patisiran and APOLLO-B Phase 3 Study in ATTR-CM

- Patisiran is an RNAi therapeutic that results in rapid knockdown of serum TTR and is approved for the treatment of hereditary ATTR (hATTR) with polyneuropathy[13]
- Patients with ATTR-CM treated with patisiran during the 12-month double-blind (DB) period of the Phase 3 APOLLO-B study (NCT03997383), demonstrated benefits in functional capacity, health status and quality of life, and in NT-proBNP and troponin I cardiac biomarkers that were sustained through an additional 12 months in the OLE period[14,15]
  - Patients completing the 12-month DB period were eligible to continue treatment in the OLE where all patients received patisiran
  - Patients who initially received placebo and switched to patisiran after 1 year displayed relative stabilization or slowing of disease progression across multiple endpoints (6-minute walk test [6MWT], Kansas City Cardiomyopathy Questionnaire–Overall Summary [KCCQ-OS], NT-proBNP, and troponin I) at Month 24
- Patisiran was well tolerated with an acceptable safety profile in patients with ATTR-CM

Objective

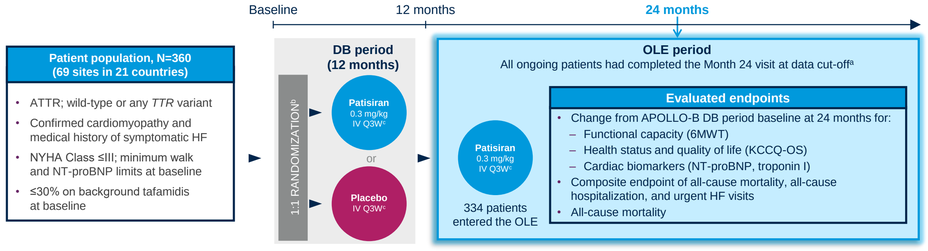
- To assess the effect of patisiran on outpatient worsening of HF, characterized by ODI, and the prognostic utility of ODI in patients with ATTR-CM

Methods

Patisiran Phase 3 APOLLO-B Study

- APOLLO-B is a global, randomized, placebo-controlled study in patients with ATTR-CM (wild-type ATTR [wtATTR] and hATTR), evaluating the efficacy and safety of patisiran in a 12-month DB period, followed by an OLE period where all patients receive patisiran (**Figure 1**)
- Data on use of outpatient diuretics were collected at baseline and throughout the study (DB period and OLE period through Month 24)
  - An outpatient worsening HF event was defined as a sustained increase (≥7 days) in average daily dose of oral loop diuretics in furosemide equivalents relative to baseline
- ODI was analyzed as time-to-first event (**Figure 2**) and as recurring events (**Figure 3**)
- All-cause mortality and CV events were analyzed using a modified Andersen–Gill model with robust variance estimator including ODI as a time-varying covariate. Patients have a value of 0 until the first occurrence of ODI, after which they have a value of 1 until the end of their follow-up

Figure 1. APOLLO-B Study Design



[a]All available efficacy and safety data through to cut-off date August 14, 2023; analysis of outcomes endpoints and safety data include all data through the data cut-off, including data beyond the Month 24 timepoint.
[b]Stratification: Background tafamidis (yes or no); hATTR vs wtATTR; NYHA Class I/II and age <75 years vs all others. [c]To reduce likelihood of infusion-related reactions, patients receive the following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; and histamine (H)1 and H2 blockers.

Results

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were generally comparable across the treatment groups (**Table 1**)
- However, patients receiving background tafamidis:
  - Had greater time from diagnosis to first dose of study drug
  - Had statistically significantly higher average daily diuretic doses at baseline (background tafamidis: n=91, mean [SD], 66.9 [81.9]; no background tafamidis: n=268, mean [SD], 46.0 [61.7]; p=0.021)

Table 1. Baseline Demographics and Disease Characteristics

	All patients		Background tafamidis		No background tafamadis	
Parameter	**Patisiran (N=181)**	**Placebo (N=178)**	**Patisiran (N=46)**	**Placebo (N=45)**	**Patisiran (N=135)**	**Placebo (N=133)**
Age, years, median (range)	76 (47–85)	76 (41–85)	76 (66–85)	75 (59–85)	76 (47–85)	76 (41–85)
Male sex, n (%)	161 (89.0)	160 (89.9)	44 (95.7)	44 (97.8)	117 (86.7)	116 (87.2)
Race, n (%)						
White	138 (76.2)	140 (78.7)	38 (82.6)	39 (86.7)	100 (74.1)	101 (75.9)
Asian	23 (12.7)	15 (8.4)	3 (6.5)	0	20 (14.8)	15 (11.3)
Black or African American	16 (8.8)	15 (8.4)	5 (10.9)	6 (13.3)	11 (8.1)	9 (6.8)
wtATTR, n (%)	144 (79.6)	144 (80.9)	41 (89.1)	40 (88.9)	103 (76.3)	104 (78.2)
Time from ATTR diagnosis to first dose of study drug, years, median (range)	0.8 (0–6)	0.4 (0–10)	2.0 (0–5)	1.7 (0–10)	0.4 (0–6)	0.3 (0–6)
NYHA Class, n (%)						
Class I	10 (5.5)	15 (8.4)	1 (2.2)	3 (6.7)	9 (6.7)	12 (9.0)
Class II	156 (86.2)	150 (84.3)	40 (87.0)	35 (77.8)	116 (85.9)	115 (86.5)
Class III	15 (8.3)	13 (7.3)	5 (10.9)	7 (15.6)	10 (7.4)	6 (4.5)
ATTR stage[a], n (%)						
Stage 1	124 (68.5)	120 (67.4)	33 (71.7)	27 (60.0)	91 (67.4)	93 (69.9)
Stage 2	46 (25.4)	45 (25.3)	9 (19.6)	16 (35.6)	37 (27.4)	29 (21.8)
Stage 3	11 (6.1)	13 (7.3)	4 (8.7)	2 (4.4)	7 (5.2)	11 (8.3)
NT-proBNP level, ng/L, median (IQR)	2008 (1135–2921)	1813 (952–3079)	1994 (1133–2665)	1964 (1107–3913)	2008 (1154–3014)	1767 (852–2835)
Daily dose of diuretics[b], mg						
Mean (SD)	48.5 (51.1)	54.2 (81.5)	57.2 (69.6)	76.9 (92.6)	45.5 (43.0)	46.6 (76.3)
Median (IQR)	40.0 (20.0–80.0)	40.0 (14.3–80.0)	40.0 (20.0–40.0)	40.0 (20.0–80.0)	40.0 (20.0–80.0)	30.0 (10.0–40.0)

[a]Patients are stratified into prognostic categories using the serum biomarkers NT-proBNP and estimated glomerular filtration rate (eGFR). Patients are categorized as follows: stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m^2; stage 2 (intermediate risk): all other patients not meeting criteria for stages 1 or 3; stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2.
[b]Average daily dose of diuretics is calculated by converting to the furosemide equivalent dose and multiplying by the frequency of use. If a patient is on no oral high-ceiling diuretics at baseline, the baseline average daily dose is 0. The conversions to furosemide equivalent doses are as follows: azosemide 60 mg = furosemide 40 mg; bumetanide 1 mg = furosemide 40 mg; and torasemide 20 mg = furosemide 40 mg.

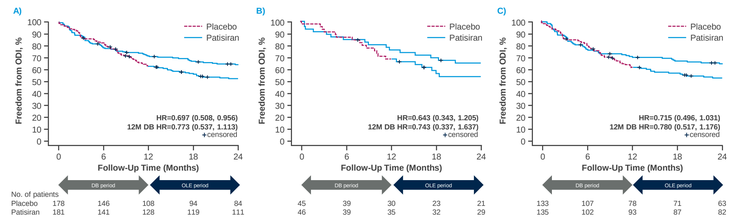
Clinical Outcomes in Patients with Outpatient HF Worsening

- In the overall population, an ODI event was associated with a subsequent increased risk of all-cause mortality, CV hospitalizations, or urgent HF visits (HR 1.357, 95% CI: 0.986, 1.869)

Impact of Patisiran on Outpatient HF Worsening

- Patients initially randomized to patisiran had fewer ODI events (68/181 [37.6%]) than placebo-randomized patients (89/178 [50.0%]) through Month 24 (i.e., 12 months DB and 12 months OLE)
- Patisiran-randomized patients had reduced outpatient worsening HF as evidenced by ODI (hazard ratio [HR] 0.697, 95% confidence interval [CI]: 0.508, 0.956), with treatment arm separation before Month 9 during the DB period (**Figure 2A**)
  - The trend in favor of patisiran was true regardless of background tafamidis use (**Figure 2B and 2C**)

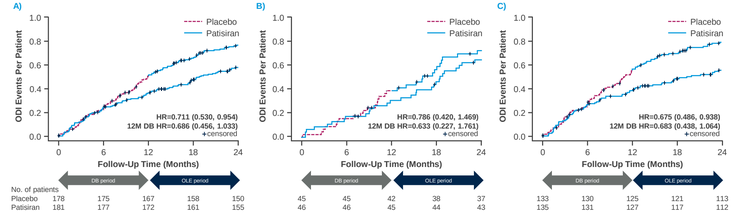
Figure 2. Kaplan–Meier Plot of Time-to-ODI over 24 Months in A) Overall Population, B) Patients on Background Tafamidis, and C) Patients Not Receiving Background Tafamidis



Figures are truncated at Month 24; events that occurred after Month 24 are included in the estimate of the HR but not shown in the figure. The HR and 95% CI for time-to-first event were estimated using Cox proportional hazards model with treatment groups as a covariate.

- The point estimate of HR for occurrence of ODI during the 24-month study period was 0.711 (95% CI: 0.530, 0.954) (**Figure 3A**)
  - The divergence between treatment groups was observed before 9 months in the DB period and maintained throughout the OLE
  - Reduction in occurrence of ODI was observed in patients not receiving background tafamidis, with a similar trend in those receiving background tafamidis (**Figure 3B and 3C**)

Figure 3. ODI Events Per Patient over 24 Months in A) Overall Population, B) Patients on Background Tafamidis, and C) Patients Not Receiving Background Tafamidis

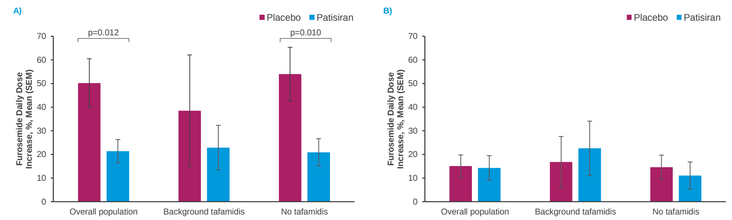


Figures show mean cumulative function of ODI events. Figures are truncated at Month 24; events that occurred after Month 24 are included in the estimate of the HR but not shown in the figure. For patients who discontinued treatment during the DB period, events occurring after Day 417 are excluded. For patients who discontinued treatment during the OLE period, events occurring more than 90 days after last patisiran dose are excluded. The HR and 95% CI for recurring events were derived using the modified Andersen–Gill model with robust variance estimator stratified by background tafamidis use, including randomized treatment arm, type of ATTR, baseline NYHA class, and age group as covariates. A HR <1 represents a favorable outcome for patisiran.

Impact of Patisiran on Daily Diuretic Dosage

- Daily diuretic dose increase was significantly greater in the placebo vs patisiran group at Month 12 (**Figure 4A**)
- There was no difference between treatment arms from Month 12 to 24 when all patients were on patisiran (**Figure 4B**)

Figure 4. Daily Diuretic Dose Increase during APOLLO-B, A) from Baseline to Month 12 (DB Period) and B) from Month 12 to Month 24 (OLE Period)



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Abbreviations: 6MWT, 6-minute walk test; ANSM, Agence nationale de sécurité du médicament et des produits de santé; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; BMI, body mass index; CI, confidence interval; CV, cardiovascular; DB, double-blind; eGFR, estimated glomerular filtration rate; H, histamine; hATTR, hereditary ATTR; HF, heart failure; HR, hazard ratio; IQR, interquartile range; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; ODI, oral diuretic initiation or intensification; OLE, open-label extension; Q3W, once every 3 weeks; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; wt, wild-type; wtATTR, wild-type ATTR.

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

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. Okumura et al. *Circulation* 2016;133:2254–62; 10. Khan et al. *Circ Heart Failure* 2021;14:e008351; 11. Ferreira et al. *Eur J Heart Fail* 2022;24:378–84; 12. Chatur et al. *Circulation* 2023;148:1735–45; 13. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. 2020. Available from: https://www.alnylam.com/wp-content/uploads/pdfs/ONPATTRO-Prescribing-Information.pdf (accessed June 23, 2023); 14. Maurer et al. *N Engl J Med* 2023;389:1553–65; 15. Maurer et al. *J Card Fail* 2024;30(1):130–1.
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