Patisiran: Concomitant Use with Tafamidis

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SUMMARY

Concomitant use of TTR stabilizers, including tafamidis, was evaluated in the patisiran Phase 2, Phase 2 OLE, and phase 3 APOLLO-B studies:

- The Phase 2 study was a multicenter, international, open-label, multiple-dose escalation study of patisiran in patients with hATTR-PN. A similar degree of TTR reduction was observed in patients receiving patisiran and concomitant TTR stabilizer therapy, including tafamidis, compared with patients not receiving concomitant TTR stabilizer therapy.[1]
- Patients who previously received and tolerated patisiran in the Phase 2 study were eligible to enroll in the Phase 2 OLE study.[2] Post-hoc analyses of the Phase 2 OLE study evaluated the safety and PD of patisiran alone or with a concomitant TTR stabilizer, including tafamidis.[3]
- In the phase 3 APOLLO study evaluating the efficacy and safety of patisiran compared with placebo in patients with hATTR-PN, the use of tafamidis was prohibited during the study. Patients must have completed a 14-day wash-out prior to the start of study drug administration.[4,5]
- In the phase 3 APOLLO-B study evaluating the efficacy and safety of patisiran versus placebo in patients with ATTR-CM, tafamidis use was permitted in patients who had tafamidis available as standard of care and were already receiving tafamidis treatment ≥6 months with disease progression in the opinion of the investigator.[6,7]
  - At baseline, 25% of patients in both the patisiran and placebo arms were receiving tafamidis. During the 12-month double-blind period, 3% of patients in the patisiran arm and 2% of patients in the placebo arm started tafamidis treatment.[6]
  - In the overall population, patisiran demonstrated a significant difference in functional capacity (6-MWT, p=0.02) and quality of life (KCCQ-OS, p=0.04) compared with placebo at 12 months.[6]
  - In subgroup analyses of patisiran compared with placebo by baseline tafamidis use, 6-MWT and KCCQ-OS results at 12 months were not statistically significant and the confidence intervals were wide for patients on tafamidis at baseline.[8]
  - Patisiran achieved a mean (±SD) reduction in serum TTR of 86.8 ± 13.6% at 12 months. The mean (±SD) reduction in serum TTR in the patisiran arm was 83.7% ± 16.3% for patients receiving tafamidis at baseline. Patisiran was shown to have a similar effect on serum TTR irrespective of baseline tafamidis use.[6]

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PHASE 2 STUDY

The Phase 2 study was a multicenter, international, open-label, multiple-dose escalation study in patients with hATTR-PN. Cohorts of 3 patients received 2 doses of patisiran, with each dose administered as an IV infusion.[1]

- Cohorts 1–3 received 2 doses of patisiran 0.01 mg/kg, 0.05 mg/kg, and 0.15 mg/kg Q4W, respectively.
- Cohorts 4 and 5 both received 2 doses of patisiran 0.3 mg/kg Q4W.
- Cohorts 6–9 all received 2 doses of patisiran 0.3 mg/kg Q3W.

The primary study objective was to evaluate the safety and tolerability of multiple ascending doses of patisiran. The secondary study objectives were to characterize the plasma and urine pharmacokinetics of patisiran and to assess preliminary evidence of the pharmacodynamic effect of patisiran on serum TTR levels.[1]

Patient Demographics & Baseline Characteristics

Patients who received concomitant tafamidis at baseline are shown in **Table 1.**[1]

Table 1. Baseline Concomitant Tafamidis Use in the Patisiran Phase 2 Study.[1,a]

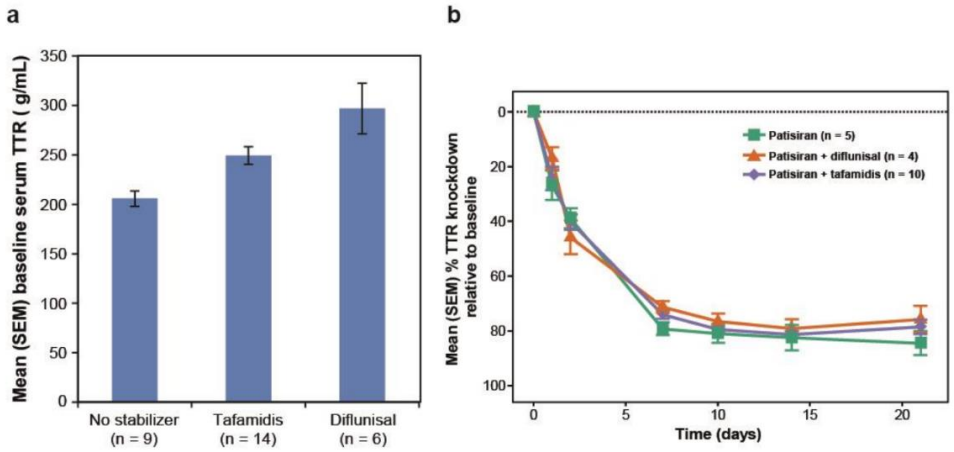
Concomitant TTR Stabilizer Use, n (%)	0.01 mg/kg Q4W (N=4)	0.05 mg/kg Q4W (N=4)	0.15 mg/kg Q4W (N=3)	0.3 mg/kg Q4W (N=7)	0.3 mg/kg Q3W (N=12)	All patients (N=29)
Tafamidis	0	1 (33.3)	2 (66.7)	4 (57.1)	7 (66.7)	14 (48.3)

Abbreviations: Q3W = every 3 weeks; Q4W = every 4 weeks; TTR = transthyretin.
[a]Intent-to-treat population.

Pharmacodynamic Results

In patients who received patisiran 0.3 mg/kg Q3W, the mean (±SD) TTR reduction from baseline at nadir was 83.8% ± 5.1% and 86.7% ± 7.0% after the first and second doses, respectively. Although patients taking a TTR stabilizer, tafamidis or diflunisal, had significantly increased baseline levels of serum TTR compared with patients not taking a TTR stabilizer ($p<0.001$ by ANOVA), patisiran administration resulted in a similar degree of TTR reduction (**Figure 1**), suggesting that concomitant TTR stabilizer use did not interfere with the pharmacodynamic activity of patisiran.[1,9]

Figure 1. TTR Reduction with Patisiran in Patients By Concomitant TTR Stabilizer Use.[9]



Abbreviations: SEM = standard error of the mean; TTR = transthyretin.
[a]Baseline TTR levels by stabilizer use (all cohorts)
[b]TTR reduction by patisiran 0.3 mg/kg cohorts; error bars represent SEM.
From Suhr et al.[9]

PHASE 2 OLE STUDY

The Phase 2 OLE study (N=27) was a multicenter, international study in patients with hATTR-PN. Patients who previously received and tolerated patisiran in the Phase 2 study were eligible to enroll in the Phase 2 OLE study. Patients received IV patisiran 0.3 mg/kg every 3 weeks for approximately 2 years. The primary objective of the Phase 2 OLE study was to evaluate the safety and tolerability of long-term dosing with patisiran. The secondary objectives were to assess the pharmacodynamic effect of long-term patisiran dosing on serum TTR levels and to monitor changes from baseline in various clinical measures.[2]

Post-hoc analyses from the Phase 2 OLE study evaluated the safety and PD of patisiran alone or with a concomitant TTR stabilizer, including tafamidis.[3]

Patient Demographics & Baseline Characteristics

Patients were permitted to receive a concomitant TTR stabilizer during the Phase 2 OLE study if the patient had started the treatment prior to study entry. Of the 27 patients enrolled in the Phase 2 OLE, 20 patients received TTR stabilizers (tafamidis [n=13], diflunisal [n=7]). One patient receiving concomitant tafamidis and 5 patients receiving concomitant diflunisal at baseline discontinued TTR stabilizer use between 1 and 18 months after entering the study.[2]

Efficacy Results

mNIS+7

In the study, neurologic function was assessed using the mNIS+7. In the total study population (N=26), a mean 6.95-point decrease (improvement) in mNIS+7 was observed at 24 months. The mean change in mNIS+7 was similar irrespective of TTR stabilizer use, which included either tafamidis or diflunisal (**Table 2**). The 6 patients who discontinued their TTR stabilizer within 18 months of entering the study did not exhibit neuropathy progression.[2]

Table 2. Change in mNIS+7 From Baseline by TTR Stabilizer Use at 24 Months.[2]

Change in mNIS+7 from baseline to Month 24	Patisiran alone (n=7)	Patisiran + TTR stabilizer (n=19)
Mean (SEM)	-6.75 (5.24)	-7.03 (2.11)
Median (range)	-8.50 (-28.50, 15.38)	-6.63 (-34.63, 3.88)

Abbreviations: mNIS+7 = modified Neuropathy Impairment Score +7; SEM = standard error of the mean; TTR = transthyretin.

Pharmacodynamic Results

The median (range) serum TTR percent change from baseline averaged over 24 months was -88.4% (-91.1 to -65.0) in patients who received patisiran alone and -79.9% (-93.3 to -74.4) in patients who received concomitant tafamidis.[3]

Safety Results

The median (range) exposure was 736 days (735-737) for the cohort with patisiran alone and 736 days (19-747) for the cohort with concomitant tafamidis. The frequencies of AEs, including severe AEs, SAEs, and AEs leading to discontinuation, are shown in **Table 3**. Most patients experienced AEs that were mild or moderate in intensity. SAEs were reported in 2 patients (28.6%) receiving patisiran alone and 4 patients (30.8%) receiving patisiran with concomitant tafamidis.[3]

Overall, in the Phase 2 OLE, safety associated with patisiran use, alone or with concomitant tafamidis, was consistent with the known safety profiles of the respective agents as monotherapy.[3]

Table 3. Safety Summary of Patients Receiving Patisiran Alone and Concomitant Tafamidis in the Phase 2 OLE Study.[3]

Event, n (%)	Patisiran alone (n=7)	Patisiran and tafamidis (n=13)
Any AE	6 (85.7)	13 (100)
Any severe AE	2 (28.6)	2 (15.4)
Any SAE	2 (28.6)	4 (30.8)
AE leading to discontinuation	1 (14.3)	0
Death	1 (14.3)[a]	0

Abbreviations: AE = adverse event; OLE = open-label extension; SAE = serious adverse event.
[a]Causes of death were myocardial infarction and gastroesophageal cancer, respectively, and both were deemed not drug-related by investigators.

APOLLO-B STUDY

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, patients received patisiran in an open-label extension period.[6]

Tafamidis use was permitted in the study in patients who had tafamidis available as local standard of care and were already receiving tafamidis treatment ≥6 months with disease progression in the opinion of the investigator.[6,8] The study design allowed for ≤30% of patients enrolled to be receiving tafamidis at baseline. Patients who were on tafamidis at baseline were encouraged, if it was medically appropriate in the opinion of the investigator, to remain on tafamidis for the duration of the double-blind period.[7]

Patient Demographics & Baseline Characteristics

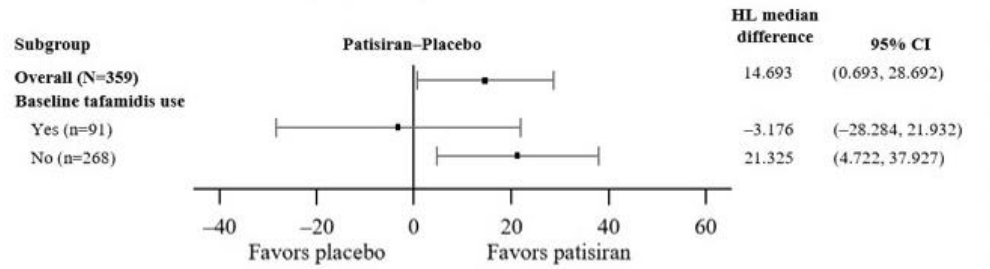
In the APOLLO-B study, 46 patients (25%) in the patisiran arm and 45 patients (25%) in the placebo arm received tafamidis at baseline. During the 12-month double-blind period, 5 patients (3%) in the patisiran arm and 3 patients (2%) in the placebo arm started tafamidis treatment. The baseline characteristics were similar between patients receiving tafamidis at baseline and those not receiving tafamidis at baseline.[6,10]

Efficacy Results

6-MWT

The median change from baseline in 6-MWT at 12 months was -8.15 m (95% CI, -16.42 to 1.50) in the patisiran arm and -21.35 m (95% CI, -34.05 to -7.52) in the placebo arm, resulting in a HL estimate of median difference of 14.69 m (95% CI, 0.69 to 28.69; p=0.02).[6] A subgroup analysis of 6-MWT by baseline tafamidis use is presented in **Figure 1**.[8]

Figure 1. Subgroup Analysis of 6-MWT by Baseline Tafamidis Use.[8]

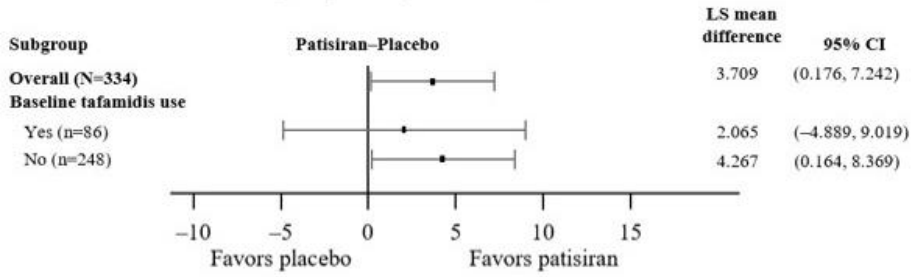


Abbreviations: 6-MWT = 6-minute walk test; CI = confidence interval; HL = Hodges-Lehmann.
From Maurer et al.[8]

KCCQ-OS

Patisiran met the first secondary endpoint of change from baseline in quality of life as measured by the KCCQ-OS score. The LS mean change from baseline in KCCQ-OS at 12 months was -3.4 points (95% CI, -5.9 to -0.9) in the placebo arm and 0.3 points (95% CI, -2.2 to 2.8) in the patisiran arm, resulting in a LS mean difference of 3.7 points (95% CI, 0.2 to 7.2; p=0.04).[6] A subgroup analysis of KCCQ-OS by baseline tafamidis use is presented in **Figure 2.**[8]

Figure 2. Subgroup Analysis of KCCQ-OS by Baseline Tafamidis Use.[8]



Abbreviations: CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares.
From Maurer et al.[8]

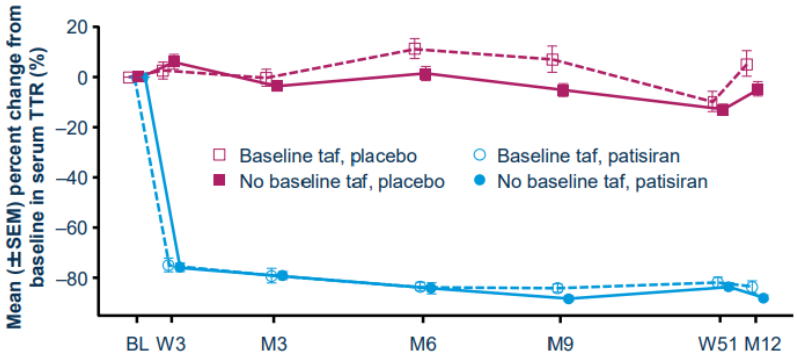
All-Cause Mortality

In the overall population, all-cause death was observed in 4 patients (2.2%) in the patisiran arm and 10 patients (5.6%) in the placebo arm (HR, 0.355; 95% CI: 0.110, 1.138). For patients receiving tafamidis at baseline, all-cause death was observed in 1 patient (2.2%) in the patisiran arm and 3 patients (6.7%) in the placebo arm (HR, 0.296; 95% CI: 0.031, 2.863). For patients not receiving tafamidis at baseline, all-cause death was observed in 3 patients (2.2%) in the patisiran arm and 7 patients (5.3%) in the placebo arm (HR, 0.396; 95% CI: 0.102, 1.538).[10]

Pharmacodynamic Results

Serum TTR reduction at 12 months was assessed as a pharmacodynamic endpoint. Patients treated with patisiran achieved a mean (±SD) serum TTR reduction of 86.8% ± 13.6%, with a similar serum TTR reduction observed irrespective of baseline tafamidis use (**Figure 3**). The mean (±SD) reduction in serum TTR in the patisiran arm was 83.7% ± 16.3% for patients receiving tafamidis at baseline and 87.9% ± 12.3% for patients not receiving tafamidis at baseline.[6]

Figure 3. Percent Change from Baseline in Serum TTR Levels.[10]



N evaluable							
BL taf, placebo	45	43	38	43	42	35	41
BL taf, patisiran	46	44	35	43	44	39	43
No BL taf, placebo	133	127	115	119	120	116	123
No BL taf, patisiran	135	125	117	121	123	105	115

Abbreviations: BL = baseline; M = month; SEM = standard error of the mean; taf = tafamidis; TTR = transthyretin; W = week.
From Maurer et al.[10]

Safety Results

Analyses of safety events by baseline tafamidis use in APOLLO-B have not been conducted; the following information presented below is from the overall patient population. AEs reported in APOLLO-B at the end of the 12-month treatment period are summarized below in **Table 4.**[6]

Table 4. APOLLO-B Summary of Adverse Events at 12 Months.[6]

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
AEs	165 (91)	168 (94)
Serious AEs	61 (34)	63 (35)
Severe AEs	47 (26)	52 (29)
AEs leading to treatment discontinuation	5 (3)	5 (3)
Deaths (safety analysis)[a]	5 (3)	8 (4)

Abbreviations: AE = adverse event; HF = heart failure.
[a]Deaths in the patisiran arm included sudden cardiac death, undetermined death, death due to COVID-19, death due to HF, and death due to pancreatitis. Efficacy analysis of deaths presented in accordance with pre-defined statistical analysis plan, which excluded deaths due to COVID-19 (1 patisiran patient) and treated cardiac transplant as death (2 placebo patients).

AEs that were reported in ≥5% of patients in the patisiran arm and seen ≥3% more frequently with patisiran compared with placebo included IRRs (12% vs. 9%), arthralgia (8% vs. 4%), and muscle spasms (7% vs. 2%).[6]

Table 5 below summarizes the cardiac safety findings from APOLLO-B, providing the number of events identified within SMQs.

Table 5. APOLLO-B Cardiac Safety Summary at 12 Months.[10]

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
Cardiac disorders (system organ class)[a]	82 (45)	100 (56)
Cardiac arrhythmia high-level group term	35 (19.3)	48 (27.0)
Supraventricular arrhythmias (including atrial fibrillation)	24 (13.3)	36 (20.2)
Ventricular arrhythmias and cardiac arrest	5 (2.8)	8 (4.5)
Cardiac conduction disorders	8 (4.4)	10 (5.6)
Rate and rhythm disorders not elsewhere classified	5 (2.8)	4 (2.2)
Cardiac failure SMQ (broad)	69 (38.1)	84 (47.2)
QT prolongation / Torsade de pointes SMQ[b]	12 (6.6)	18 (10.1)

Abbreviations: QT = QT interval; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.
[a]Based on MedDRA "Cardiac Disorders" System Organ Class.
[b]There were no identified cases of Torsade de pointes.

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ANOVA = analysis of variance; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HF = heart failure; HL = Hodges-Lehmann; HR = hazard ratio; IRR = infusion-related reaction; IV = intravenous; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; MedDRA = Medical Dictionaries for Regulatory Activities; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamics; Q3W = every 3 weeks; Q4W = every 4 weeks; QT = QT interval; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SMQ = standardized MedDRA Query; taf = tafamidis; TTR = transthyretin; W = week; wtATTR = wild-type transthyretin amyloidosis.

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