Indirect Comparison Of Patisiran and Tafamidis For Treatment Of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis With Polyneuropathy

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening, multi-systemic disease caused by mutations in the transthyretin (TTR) gene resulting in debilitating morbidity and high mortality[1-3]
  - Cardinal manifestations are polyneuropathy and cardiomyopathy
  - Median survival of 4.7 years following diagnosis and further reduced to 3.4 years for those with cardiomyopathy[3-5]

Patisiran

- Investigational RNAi therapeutic
- Evaluated in a randomized, placebo-controlled Phase 3 APOLLO study (NCT01960348) and showed significant improvement in primary endpoint Modified-Neuropathy Impairment Score +7 (mNIS+7) and secondary endpoint Norfolk Quality of Life (Norfolk QOL-DN) compared to placebo and was generally well tolerated

Tafamidis

- TTR tetramer stabilizer
- Approved in Europe and select countries for the treatment of transthyretin amyloidosis; in the European Union it has been approved specifically for the treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment[6-8]
- In the Phase 3 placebo-controlled study (Fx-005; NCT00409175), the co-primary endpoints of Neuropathy Impairment Score of the Lower Limbs (NIS-LL) response (<2 increase in NIS-LL) and Norfolk QOL-DN were not statistically significantly different from placebo in the intention-to-treat (ITT) population at 18 months[9,10]
- Statistically significant treatment effects were observed for co-primary endpoints (NIS-LL response and Norfolk QOL-DN) in the smaller, efficacy-evaluable population, comprised of patients who completed the study as per protocol[9]

Objective

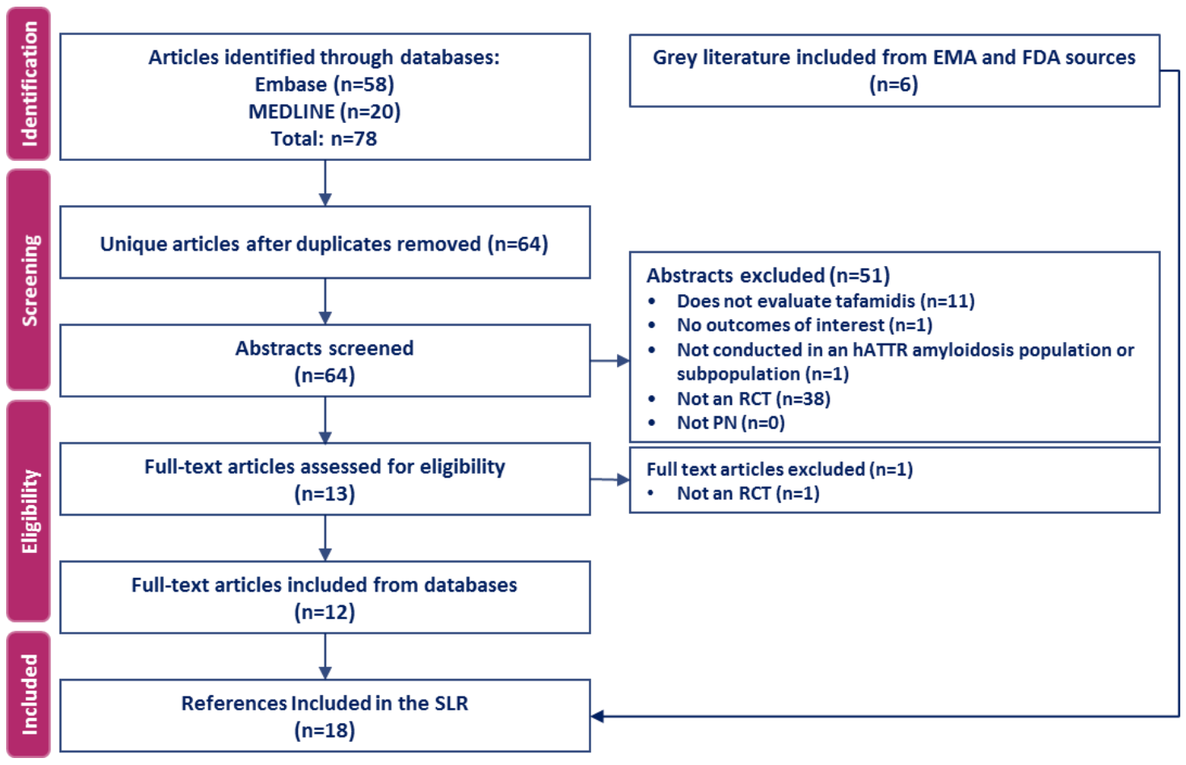
- Indirect treatment comparison (ITC) enables the comparison of therapies using a common comparator
  - Method can be used to inform healthcare decision making, as clinical trials rarely directly compare all treatments of interest[11,12]
- In the absence of direct comparative data, the objective of this analysis was to evaluate the comparative efficacy of tafamidis and patisiran in hATTR amyloidosis using ITC

Methods

Systematic Literature Review (SLR)

- A systematic literature review (SLR) was conducted to identify all publications on randomized controlled trials (RCT) for tafamidis
- Procedure followed established best methods for SLRs in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13] (Figure 1)
- Eligibility required randomized controlled trials comparing tafamidis to placebo and included efficacy endpoints
- Single-arm and observational trials were not included, as indirect comparison methodologies typically require randomized controlled data

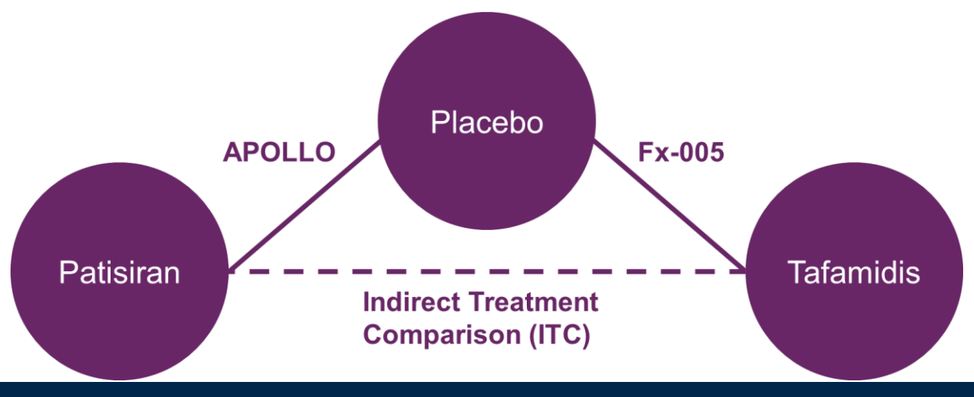
Figure 1. Tafamidis SLR algorithm based on PRISMA guidelines



Statistical approach for ITC

- ITCs were conducted for all endpoints measured across both trials: change from baseline in NIS-LL, NIS-LL response, Norfolk QOL-DN, and modified Body Mass Index (mBMI)
- ITCs were performed using the standard pairwise Bucher method to estimate the relative efficacy of patisiran to tafamidis from baseline to 18 months (Figure 2)
  - Method compares the magnitude of treatment effect in each trial by evaluating the differences between treatment and placebo arms (i.e., mean differences, odds ratios)
  - Preserves the original randomization in the trial population
- In APOLLO, mean change in Norfolk QOL-DN and mBMI were a priori outcomes; mean change in NIS-LL was derived from components of the NIS+7 (an a priori outcome), and NIS-LL response was calculated post-hoc

Figure 2: Standard pairwise Bucher method



Methods (cont.)

APOLLO and Fx-005 populations (Table 1)

- The Stage 1 disease subgroup was used as the base-case analysis to balance similarity with the Fx-005 population and sample size considerations
- Due to differences in trial demographics, sensitivity analyses were performed on remaining subgroups to match APOLLO patients to Fx-005 (Stage 1 , Stage 1 and V30M, Stage 1 and treatment-naïve, all)

Table 1: APOLLO and Fx-005 baseline demographics

Baseline Characteristics	APOLLO (patisiran)		Fx-005[9] (tafamidis)	
	Patisiran (n = 148)	Placebo (n = 77)	Tafamidis (n = 64)	Placebo (n = 61)
Age, mean (SD)	59.6 (11.96)	62.2 (10.76)	39.8 (12.7)	38.4 (12.9)
Males, %	73.6%	75.3%	50%	42.6%
V30M, %	37.8%	51.9%	100%	100%
NIS-LL, mean (SD)	36.79 (18.20)	34.79 (17.83)	8.4 (11.40)	11.4 (13.54)
mBMI, mean (SD)	969.7 (210.45)	989.9 (214.19)	1004.6 (165.20)	1011.5 (212.92)
FAP Stage	I: 45.3%; II: 54.7%; III: 0%	I: 48.1%; II: 50.6%; III: 1.3%	I: 100% (assumed)	I: 100% (assumed)

Results

Systematic Literature Review (SLR)

- Identified 18 publications describing one randomized, placebo-controlled clinical trial of tafamidis versus placebo (Fx-005) in patients with hATTR amyloidosis

ITC

- Overall, the results of analyses suggest patisiran had a greater treatment effect over tafamidis, and in many cases, these effects were statistically significant (Table 2)

Table 2: APOLLO (patisiran) & Fx-005 (tafamidis) efficacy outcomes †

		Patisiran vs. Placebo (Mean Difference & Standard Error)	Tafamidis vs. Placebo (Mean Difference & Standard Error)	Patisiran vs. Tafamidis (Mean Difference & 95% Confidence Interval)
NIS-LL	**Stage 1**	-8.2 [1.9]	-2.7 [1.3]	-5.5 [-10.0, -1.0]*
	Stage 1, V30M	-9.9 [2.1]		-7.2 [-12.1, -2.3]*
	Stage 1, Tx-Naïve	-9.4 [3.2]		-6.7 [-13.6, 0.1]
	All	-11.2 [1.4]		-8.5 [-12.3, -4.7]*
NIS-LL Response (Odds Ratio)	**Stage 1**	6.4 [0.5]	2.0 [0.4]	3.2 [0.9, 11.3]
	Stage 1, V30M	22.5 [1.1]		11.4 [1.2, 111.5]*
	Stage 1, Tx-Naïve	5.7 [0.7]		2.9 [0.6, 14.2]
	All	8.5 [0.4]		4.3 [1.5, 12.7]*
Norfolk QOL-DN	**Stage 1**	-18.3 [4.2]	-5.2 [3.3]	-13.1 [-23.6, -2.7]*
	Stage 1, V30M	-18.9 [6.6]		-13.7 [-28.2, 0.8]
	Stage 1, Tx-Naïve	-24.2 [6.2]		-19.0 [-32.8, -5.2]*
	All	-21.1 [3.1]		-15.9 [-24.8, -7.0]*
mBMI	**Stage 1**	120.5 [22.8]	73.1 [16.5]	47.4 [-7.7, 102.5]
	Stage 1, V30M	117.0 [38.0]		43.9 [-37.3, 125.1]
	Stage 1, Tx-Naïve	142.2 [42.6]		69.1 [-20.3, 158.5]
	All	115.7 [16.9]		42.6 [-3.7, 88.9]

Blue text indicates result favors patisiran; pink text indicates result favors tafamidis

*Indicates statistical significance (Confidence Interval does not cross 0 for mean differences, or 1 for odds ratios)

†Sample size (n) patisiran v. placebo: Stage 1: patisiran 67, placebo 37; Stage 1, V30M: patisiran 24, placebo 20; Stage 1, Tx-naïve: patisiran 31, placebo 17; all: patisiran 148, placebo 77
Sample size (n) tafamidis v. placebo: tafamidis 64, placebo 61

Safety *(not compared as part of this analysis)*

- Each treatment considered to be generally well tolerated, with low rates of discontinuations due to adverse events (AEs) (Table 3)
- In each trial, the frequency of AEs and Serious AEs (SAEs) were similar between treatment and placebo

Table 3: Key safety outcomes in APOLLO (patisiran) and Fx-005 (tafamidis)

	APOLLO (patisiran)		Fx-005 (tafamidis)	
% of patients	**Patisiran**	**Placebo**	**Tafamidis**	**Placebo**
Any AEs	96.6	97.4	92.3	96.8
SAEs	36.5	40.3	9.2	7.9
AEs Leading to Discontinuation	4.7	14.3	6.2	4.8
Deaths	4.7	7.8	3.1	4.8

Limitations

- Indirect comparisons can be biased if differences in patient and disease characteristics between trials are effect modifiers (i.e., the relative treatment effect between arms is influenced by a third variable)[14]

Conclusions

- This indirect comparison suggests a benefit of patisiran versus tafamidis in Stage 1 polyneuropathy for patients with hereditary transthyretin (hATTR) amyloidosis
  - This benefit was observed across all endpoints assessed, across the base-case analysis and all sensitivity analyses, and in many cases the difference was statistically significant

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Abbreviations: TTR, transthyretin; hATTR, hereditary transthyretin; mNIS+7, Modified-Neuropathy Impairment Score +7; Norfolk-QoL-DN, Norfolk Quality of Life; NIS-LL, Neuropathy Impairment of the Lower Limbs; ITT, Intent-to-treat; ITC, Indirect Treatment Comparison; RCT, Randomized Controlled Trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; mBMI, modified Body Mass Index; FAP, Familial Amyloid Polyneuropathy.
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