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A Multi-Method Approach to an Indirect Treatment Comparison of Eplontersen and Vutrisiran for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Introduction

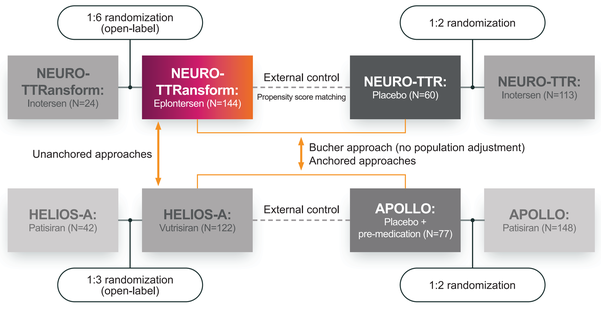
- Hereditary transthyretin-mediated amyloidosis with polyneuropathy (ATTRv-PN) is a rare, fatal neuropathy caused by transthyretin (TTR) gene mutations, leading to accumulation of ATTR amyloid in multiple tissues including the peripheral nervous system.[1,2] This causes rapidly progressive, disabling polyneuropathy and profound impairment of quality of life.[3,4]
- Gene silencers targeting TTR include vutrisiran (recently approved by the FDA and EMA) and eplontersen, which is in development.
- Eplontersen, an antisense oligonucleotide, is being evaluated in the phase III NEURO-TTRansform clinical trial (NCT04136184) using an external placebo from the phase III NEURO-TTR trial (NCT01737398).[5] In a planned interim analysis at week 35, versus external placebo:
  - Eplontersen met its co-primary efficacy endpoints of difference in percent change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) composite score and percent change from baseline in serum TTR. Eplontersen also demonstrated a favorable safety and tolerability profile.[6]
  - Eplontersen also met its key secondary efficacy endpoint of difference in change from baseline in Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) total score.[6,7] Norfolk QoL-DN is a co-primary endpoint at week 66.[5]
- Vutrisiran, a recently approved TTR silencer therapy, met the primary endpoint of change from baseline in mNIS+7, and all secondary efficacy endpoints, in the phase III HELIOS-A (NCT03759379) trial.[8]
- The mean serum TTR reduction from baseline was 81% in the NEURO-TTRansform eplontersen arm at week 35 and 81% in the HELIOS-A vutrisiran arm at month 9.[6,8,9]
- Comparative efficacy between eplontersen and vutrisiran has not been evaluated in a head-to-head study.
- The objective of this study was to evaluate the feasibility of indirect treatment comparisons (ITCs) and implications on interpretation of ITC results between eplontersen and vutrisiran at week 39 (approximately 9 months).

Methods

Data sources and ITC methods

- For eplontersen, individual patient data (IPD) from the NEURO-TTRansform trial[5] and NEURO-TTR trial[10] at week 35 were available, while aggregate data were available for vutrisiran from the HELIOS-A trial[8] and the APOLLO (NCT01960348) trial[11] at 9 months (Figure 1).

Figure 1. Data sources and ITC methods[5,8,10-12]



ITC, indirect treatment comparison

- Feasibility was evaluated for Bucher, anchored and unanchored approaches based on the capabilities and assumptions of each ITC method (Table 1).[12]

Table 1. ITC methods

	Bucher[12]	Anchored STC/MAIC[12]	Unanchored STC/MAIC[12]
Control arm	Assumes a common control arm		Common control arm not required
Distribution of TEMs	Assumes balanced TEMs	No requirement for balanced TEMs	
Trial design	Possible to **partially account for differences in timepoint** and **missing data handling method**	Possible to **partially account for differences in some eligibility criteria**, **timepoint** and **missing data handling method**	

ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; TEM, treatment effect modifier; STC, simulated treatment comparison

- Simulated treatment comparison (STC) and matching adjusted indirect comparison (MAIC) methods were considered for both anchored and unanchored comparisons.
  - Models were created to adjust for pre-specified treatment effect modifiers (TEMs) and prognostic factors for STC and MAIC. The Reference model adjusted for all pre-specified TEMs and prognostic factors (age, sex, race (white/non-white), FAP stage, V30M mutation, prior stabilization treatment, cardiac involvement, and baseline Norfolk QoL-DN total score). The Alternative model adjusted for a reduced number of variables (FAP stage and baseline Norfolk QoL-DN total score); these were arrived at using stepwise selection based on AIC.

Endpoints and data handing

- Feasibility of comparing Norfolk QoL-DN and mNIS+7 endpoints was assessed.
- Change from baseline at week 35 in NEURO-TTRansform IPD was extrapolated to week 39 (approximately 9 months), assuming a constant rate of change.
- The variables used in the multiple imputation of missing data in HELIOS-A were applied for multiple imputation of missing data in NEURO-TTRansform IPD.

Results

- Unanchored approaches are most appropriate for ITC between eplontersen and vutrisiran. Table 2 shows how each method is (✓) or is not (✗) able to address differences between the trials.

Table 2. ITC feasibility assessment

	NEURO-TTRansform NEURO-TTR	HELIOS-A APOLLO	Bucher	Anchored STC/MAIC	Unanchored STC/MAIC
Eligibility criteria	Differences in baseline NIS and KPS[a]		✗	✓	✓
Distribution of potential TEMs	Different (see table 3)		✗	✓	✓
Common control arm	No common control arm; pre-medication used in APOLLO placebo arm		✗	✗	✓

[a]NIS: NEURO-TTRansform ≥ 10 and ≤ 130, HELIOS-A 5–130; KPS: NEURO-TTRansform > 50, HELIOS-A ≥ 60.

ITC, indirect treatment comparison; KPS, Karnofsky performance status; MAIC, matching adjusted indirect comparison; NIS, neurologic impairment score; STC, simulated treatment comparison; TEM, treatment effect modifier

- The Bucher method was not appropriate because the assumption of balanced TEMs was violated. Furthermore, neither the Bucher nor anchored ITC methods were appropriate because the assumption of a common control arm was violated by the use of pre-medication in the APOLLO placebo arm, as pre-medication could impact trial endpoints.
  - Patients in the external placebo arm from APOLLO used for the comparison with vutrisiran in HELIOS-A received pre-medication consisting of intravenous (IV) dexamethasone (10 mg), oral paracetamol (500 mg), IV H2 blocker, and IV H1 blocker at least 60 min prior to each 3-weekly IV infusion of placebo.
- For the unanchored comparisons, baseline patient characteristics in the NEURO-TTRansform eplontersen arm were adjusted to match those in the HELIOS-A vutrisiran arm (Table 3).

Table 3. Potential treatment effect modifiers and prognostic factors at baseline in the eplontersen arm before and after population adjustment to match the vutrisiran arm

	Eplontersen (n = 144) Before matching	Eplontersen After matching[a,b]	Vutrisiran (n = 122)
Age (years), mean (SD)	**53.0** (15.0)	**57.8** (14.8)	**57.8** (13.2)
Male sex %	**69.4**	**64.8**	**64.8**
Race, %			
White	**78.3**	**70.5**	**70.5**
Non-white	**21.7**	**29.5**	**29.5**
V30M mutation, %	**59.0**	**44.3**	**44.3**
Cardiac involvement, %	**14.6**	**32.8**	**32.8**
Previous treatment with tafamidis or diflunisal, %	**69.4**	**61.5**	**61.5**
FAP stage, %			
Stage 1	**79.9**	**70.0**	**70.0**
Stage 2	**20.1**	**30.0**	**30.0**
Norfolk QoL-DN total score at baseline, mean (SD)	**44.1** (26.6)	**47.1** (26.4)	**47.1** (26.3)

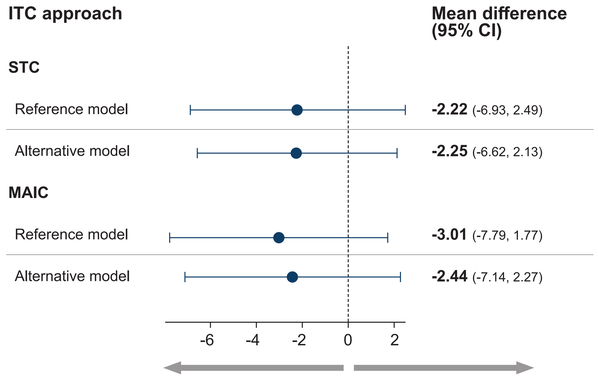
[a]Reweighting in the table is based on the Reference model.

[b]After population adjustment through reweighting to match baseline characteristics of the vutrisiran group, the effective sample size in the eplontersen group was 93 patients.

FAP, familial amyloidosis polyneuropathy; SD, standard deviation

- Different versions of mNIS+7 were used in the eplontersen and vutrisiran trial programmes.[13] No ITC of the mNIS+7 composite score was performed as it was not possible to achieve identical scales due to the lack of components.

Figure 2. Unanchored ITC of change from baseline in Norfolk QoL-DN at week 39 (approximately 9 months)



CI, confidence interval; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; STC, simulated treatment comparison

- The unanchored ITC showed no statistically significant difference between eplontersen and vutrisiran in change from baseline in Norfolk QoL-DN total score at week 39 (approximately 9 months) (Figure 2).

Conclusions

- The unanchored approaches for ITC between eplontersen and vutrisiran are the most appropriate methods, as they do not require a common control arm and can partially account for key differences between trials.
- Bucher and anchored approaches should not be used for ITC between eplontersen and vutrisiran because key assumptions for these ITC approaches are violated by the lack of a common control arm and differences in potential TEMs and prognostic factors at baseline in the trials.
- ITC of the Norfolk QoL-DN endpoint was performed as the exact same instrument was used in NEURO-TTRansform and HELIOS-A. In contrast, ITC of the mNIS+7 endpoint was not performed because different versions of mNIS+7 were used in the two trials making it impossible to achieve identical scales due to the lack of components.
- The results from unanchored STC and unanchored MAIC of eplontersen and vutrisiran did not show a statistically significant difference between their effects on change from baseline in Norfolk QoL-DN total score at week 39.

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