Simulated Treatment Comparison and Matching-Adjusted Indirect Comparison of the Efficacy of Eplontersen and Vutrisiran for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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neuro TTRansform

Poster # CO183

Introduction

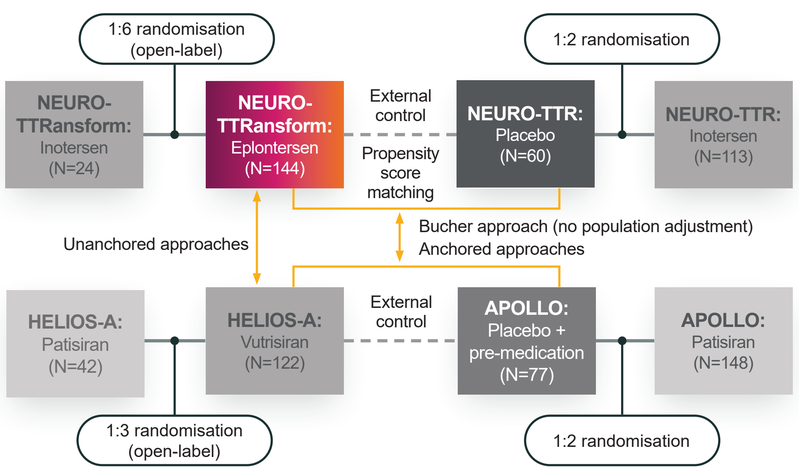
- Hereditary transthyretin-mediated amyloidosis with polyneuropathy is a rare, fatal disease in which the transthyretin (TTR) gene is mutated, leading to amyloid deposition in multiple tissues[1,2]
- Build up of amyloid in the peripheral nervous system causes rapidly progressive neuropathy and multisystem disability, which profoundly impact quality of life[3,4]
- Targeted gene silencers for TTR include eplontersen (currently in development), and vutrisiran (approved by FDA[5] and EMA[6])
- Eplontersen was evaluated in the phase 3 NEURO-TTRansform trial (NCT04136184),[7] versus an external placebo group from the phase 3 NEURO-TTR trial (NCT01737398)[8]
  - At the planned Week 35 interim analysis, eplontersen met its co-primary endpoints of percent change from baseline in serum TTR and change from baseline in modified Neuropathy Impairment Score (mNIS+7) composite score, and key secondary efficacy endpoint of change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, and demonstrated a favourable safety profile[9]
  - At the final Week 66 timepoint, the co-primary endpoints of percent change from baseline in serum TTR, change from baseline in mNIS+7 composite score, and change from baseline in Norfolk QoL-DN were not formally re-tested and remained consistent with interim analysis results[10]
- Vutrisiran met its primary endpoint of change from baseline in mNIS+7 and all secondary efficacy endpoints in the phase 3 HELIOS-A trial (NCT03759379)[11]
- Comparative efficacy between eplontersen and vutrisiran has not been evaluated in a head-to-head study; clinicians must rely on indirect treatment comparisons (ITCs) for decision-making[12]
- The objective of this study was to evaluate the strengths and weaknesses of common ITC methods and to perform an ITC using the most appropriate methods between the eplontersen Week 35 interim analysis from NEURO-TTRansform and vutrisiran month 9 data from HELIOS-A

Methods

Data sources and ITC methods

- Individual patient data (IPD) for eplontersen were available from NEURO-TTRansform[7] and NEURO-TTR[8] at Week 35 (Figure 1)
- Aggregate data were available for vutrisiran from HELIOS-A[11] and APOLLO[13] at 9 months (Figure 1)

Figure 1. Data sources and ITC methods[7-9, 11, 13-14]



ITC, indirect treatment comparison

- Appropriateness of Bucher, anchored, and unanchored approaches was assessed (Table 1; tick ✓ indicates ITC method can address differences between trials, cross ✗ indicates method is unable to address differences between trials)[14]

Table 1. Results of 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 2)	✗	✓	✓
Common control arm	No common control arm; pre-medication used in APOLLO placebo arm	✗	✗	✓

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

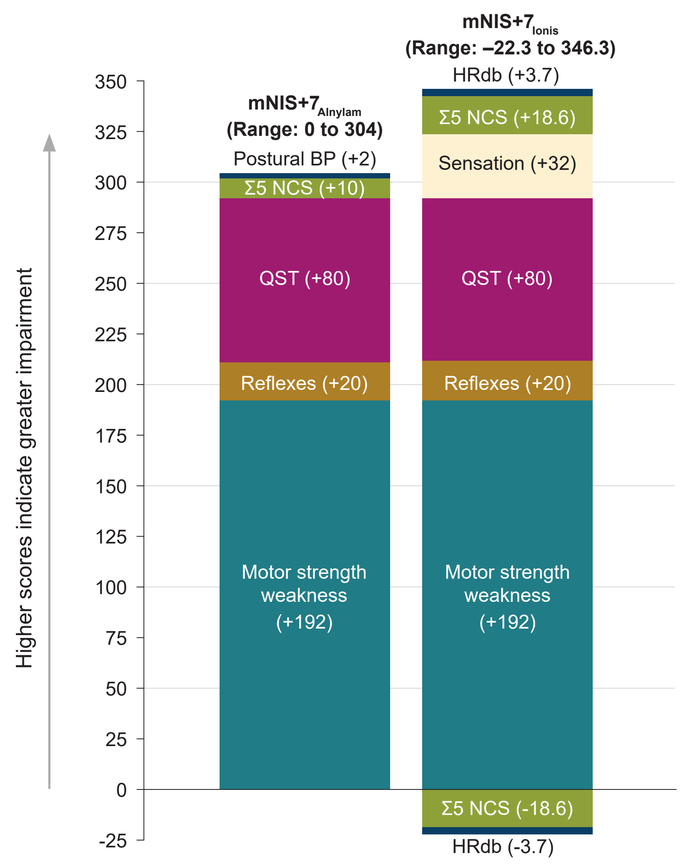
ITC, indirect treatment comparison; KPS, Karnofsky performance status; MAIC, matching adjusted indirect comparison; NIS, neurologic impairment score; STC, simulated treatment comparison; TEM, treatment effect modifier

- The Bucher method was not appropriate because potential treatment effect modifiers (TEMs) were not balanced
- 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
- Therefore, unanchored methods were considered most appropriate

Endpoints

- The Norfolk QoL-DN instrument is comparable between studies
- The mNIS+7 version used in NEURO-TTRansform and NEURO-TTR ($mNIS+7_{Ionis}$) differs from that used in HELIOS-A and APOLLO ($mNIS+7_{Alnylam}$) in terms of components and scoring[15] (Figure 2)
- Therefore, $mNIS+7_{Ionis}$ was rescored to approximate $mNIS+7_{Alnylam}$

Figure 2. Comparison of $mNIS+7_{Alnylam}$ and $mNIS+7_{Ionis}$



BP, blood pressure; HRdb, Heart rate while deep breathing; NCS, nerve conduction studies; QST, quantitative sensory testing

Rescoring mNIS+7

- Rescoring of $mNIS+7_{Ionis}$ required the following:
  - Exclusion of the sensation component, which is not included in $mNIS+7_{Alnylam}$
  - Rescoring the items in the nerve conduction studies (NCS) component based on the 95th and 99th percentiles of a healthy reference population, as 0 (no impairment), 1 (mild impairment), or 2 (severe impairment)
  - Mapping the heart rate with deep breathing (HRdb) component of $mNIS+7_{Ionis}$ to the postural blood pressure (BP) component in $mNIS+7_{Alnylam}$ by rescoring it based on the 95th and 99th percentiles of a healthy reference population, as 0 (no impairment), 1 (mild impairment), or 2 (severe impairment)

Data handling

- 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 visit-level missing data in HELIOS-A were applied for multiple imputation of missing data in NEURO-TTRansform IPD

Models

- Simulated treatment comparison (STC) and matching adjusted indirect comparison (MAIC) methods were used for unanchored comparisons
- Models were created to adjust for pre-specified TEMs and prognostic factors (PFs) for STC and MAIC
  - The Reference model adjusted for all pre-specified TEMs and PFs (age, sex, race (white/non-white), familial amyloid polyneuropathy (FAP) stage, V30M mutation, prior TTR stabiliser treatment, cardiac involvement, and endpoint score at baseline)
  - The Alternative models adjusted for a reduced number of variables, chosen by stepwise selection based on Akaike information criterion:
    - Norfolk QoL-DN: FAP stage, V30M mutation and baseline Norfolk QoL-DN total score;
    - mNIS+7: sex, prior TTR stabiliser treatment and baseline mNIS+7 composite score

Results

- For unanchored comparisons, baseline patient characteristics from the NEURO-TTRansform eplontersen arm were adjusted to match those in the HELIOS-A vutrisiran arm (Table 2)

Table 2. TEMs and PFs at baseline in the eplontersen arm before and after population adjustment to match the vutrisiran arm for Norfolk QoL-DN

	Eplontersen (n = 144) Before matching	Eplontersen After matching[a,b]	Vutrisiran (n = 122)
Age (years), mean (SD)	**52.5** (15.0)	**57.8** (14.4)	**57.8** (13.2)
Male sex %	**69.4**	**64.8**	**64.8**
Race, (white), %	**77.8**	**70.5**	**70.5**
V30M mutation, %	**59.0**	**44.3**	**44.3**
Cardiac involvement,[c] %	**17.0**	**32.8**	**32.8**
Prior TTR stabiliser treatment, %	**69.4**	**61.5**	**61.5**
FAP stage 1, %	**79.8**	**69.7**	**69.7**
FAP stage 2, %	**20.2**	**30.3**	**30.3**
Norfolk QoL-DN total score at baseline, mean (SD)	**43.0** (25.7)	**47.1** (26.4)	**47.1** (26.3)

[a] After population adjustment through reweighting to match baseline characteristics of the vutrisiran group, the effective sample size in the eplontersen group was 98 patients for the Norfolk QoL-DN endpoint

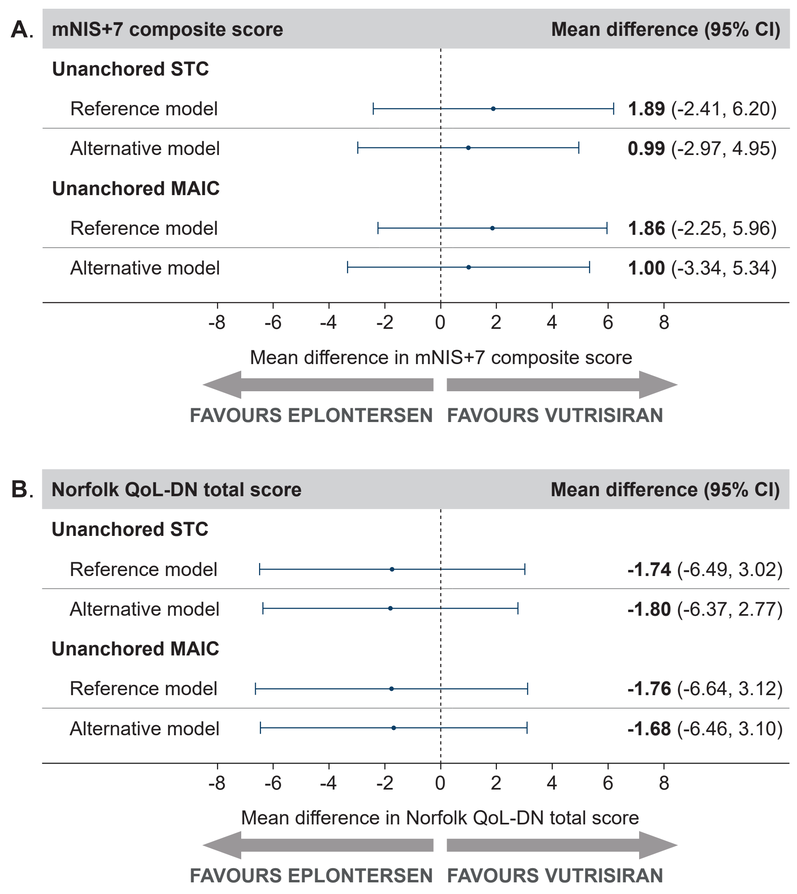
[b] Values presented are for the reference model generated for the Norfolk QoL-DN endpoint. Values were similar for the mNIS+7 endpoint, with minor differences due to missing data. Baseline mNIS+7 composite score was 60.5 in the original eplontersen data, 60.6 in the aggregated vutrisiran data, and 60.6 in the matched reference model for that endpoint, which had an effective sample size of 95 patients.

[c] As defined in HELIOS-A

FAP, familial amyloidosis polyneuropathy; PF, prognostic factor; SD, standard deviation; TEM, treatment effect modifier; TTR, transthyretin

- The unanchored ITC showed no statistically significant difference between eplontersen and vutrisiran in change from baseline in mNIS+7 composite score (Figure 3a) or Norfolk QoL-DN total score (Figure 3b) at Week 39

Figure 3. Mean difference in change from baseline in **A**. mNIS+7 composite score and **B**. Norfolk QoL-DN total score between eplontersen and vutrisiran using unanchored ITC methods



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

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 PFs at baseline in the trials
- Due to differences in the mNIS+7 versions between the eplontersen and vutrisiran trial programmes, rescoring of the mNIS+7 composite score was performed to improve comparability of the ITC
- Both unanchored STC and unanchored MAIC showed no statistically significant difference in mNIS+7 composite score and Norfolk QoL-DN total score between eplontersen and vutrisiran, suggesting they have broadly equivalent treatment effect over the course of 39 weeks

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Acknowledgements: The NEURO-TTRansform study is sponsored by Ionis Pharmaceuticals. The current work was supported by AstraZeneca, who provided support for data analysis and medical writing. Medical writing support was provided by Kerrie Ford and Carla De Villiers of Health Economics and Outcomes Research Limited.