NfL Levels Significantly Decrease in Response to Treatment with Patisiran or Vutrisiran in hATTR Amyloidosis with Polyneuropathy

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Summary

- **In the HELIOS-A study, NfL levels significantly decreased as early as 4 months following initiation of the RNAi therapeutics vutrisiran or patisiran, and these reductions from baseline were maintained through 18 months of treatment**
  - **The observed decreases in NfL levels following treatment in HELIOS-A were consistent with the results in patisiran-treated patients from APOLLO**
  - **In contrast, NfL levels significantly increased in placebo treated patients from APOLLO as early as 4 months and continued to increase over 18 months**
- **Baseline NfL levels were positively correlated with baseline mNIS+7 scores in HELIOS-A, suggestive of NfL being an indicator of disease severity**
- **Changes from baseline in NfL levels and mNIS+7 at 18 months were also positively correlated across HELIOS-A and APOLLO, which suggest that the degree of reduction of NfL may be associated with the level of improvement in polyneuropathy**
- **These results collectively support the utility of NfL as a biomarker of disease severity, disease progression, and treatment response over time, and provide biological evidence that reinforces the demonstrated clinical efficacy of patisiran and vutrisiran in patients with hATTR amyloidosis with polyneuropathy**

Background and Rationale

hATTR Amyloidosis

- A rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by variants in the *TTR* gene[1–5]
- Diagnosis is difficult and often delayed,[6,7] and monitoring disease progression and treatment response can be challenging[8–13]

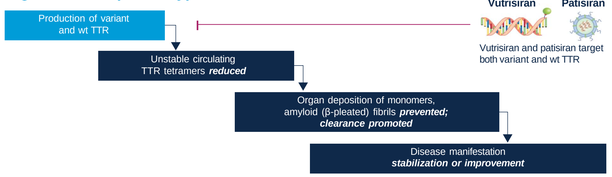
Neurofilament Light Chain (NfL)

- An abundant, highly conserved, neuron-specific, structural neurofilament protein[14]
- Elevated plasma NfL levels are seen in various diseases presenting with neuropathy,[15–22] presumed to result from NfL release following neuroaxonal injury, making NfL a biomarker for nerve damage[23,24]
- Reliable quantitative measurements of blood NfL levels are now possible in the clinic
- NfL has been proposed as a potential biomarker of disease progression and treatment response in patients with hATTR amyloidosis with polyneuropathy[25,26]

Objective

- To characterize the effect of the RNAi therapeutics (**Figure 1**) vutrisiran and patisiran on NfL levels in hATTR amyloidosis with polyneuropathy and further assess the potential utility of NfL to monitor disease progression and treatment response

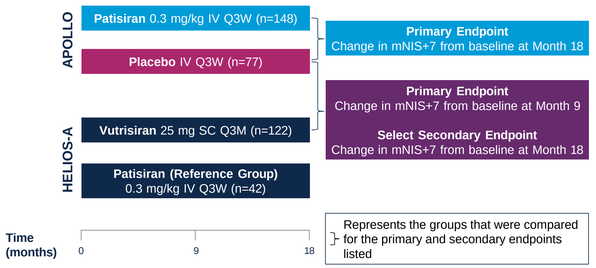
Figure 1. Therapeutic Hypothesis



Methods

- Patients enrolled in the APOLLO or HELIOS-A studies were included in this post hoc analysis if they had sufficient plasma sample for biomarker investigation and consented to the use of their sample (**Figure 2**)
- Samples were also collected in healthy controls who were age- and sex-matched to the APOLLO population to provide a reference for NfL levels in individuals without hATTR amyloidosis
- NfL plasma levels were measured in duplicate in healthy controls and in patients with hATTR amyloidosis with polyneuropathy using the Quanterix® Simoa™ platform
- Quantitative NfL analyses were conducted in the double-blind APOLLO study at baseline, 21 days, 4 months, and 18 months in placebo and patisiran groups
- Quantitative NfL analyses were conducted in the open-label HELIOS-A study at baseline, 43 days, 4 months, 9 months, and 18 months in vutrisiran and patisiran groups

Figure 2. Treatment Arms of the APOLLO and HELIOS-A Studies



Results

Baseline Characteristics of Patients with NfL Assessments

- Baseline demographics and characteristics for the subset of patients from the APOLLO and HELIOS-A studies with NfL assessments are shown in **Table 1**
- Overall, the HELIOS-A and APOLLO patient populations were widely overlapping and clinically comparable

Table 1. Baseline Demographics and Characteristics

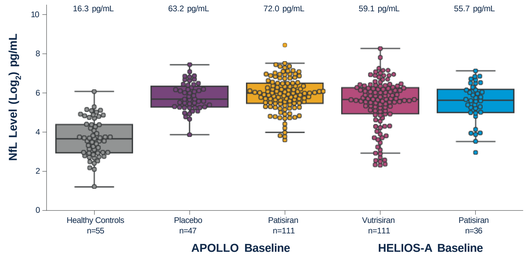
Characteristic	APOLLO		HELIOS-A	
	Placebo (n=47)	Patisiran (n=111)	Vutrisiran (n=111)	Patisiran (n=36)
Age (years), median (range)	64 (34–80)	63 (27–83)	60 (31–81)	61 (31–81)
Male, n (%)	36 (77)	85 (77)	69 (62)	23 (64)
***TTR* genotype, n (%)**				
V30M	24 (51)	47 (42)	48 (43)	16 (44)
Non-V30M	23 (49)	64 (58)	63 (57)	20 (56)
Prior TTR stabilizer use, n (%)	25 (53)	65 (59)	66 (59)	29 (81)
NIS, mean (range)	55.9 (7–119)	60.5 (6–142)	42.4 (5–127)	44 (5.5–115.6)
mNIS+7, mean (range)	74.1 (17–151)	80.9 (8–163)	60.1 (2.5–158)	60.9 (7–137.6)
PND score, n (%)				
I: preserved walking, sensory disturbances	11 (23)	24 (22)	42 (38)	14 (39)
II: impaired walking but can walk without stick or crutch	17 (36)	32 (29)	44 (40)	14 (39)
IIIA: walk with 1 stick or crutch	13 (28)	33 (30)	13 (12)	5 (14)
IIIB: walk with 2 sticks or crutches	6 (13)	22 (20)	12 (11)	3 (8)

Results (cont'd)

Baseline NfL Levels of Patients in APOLLO and HELIOS-A

- NfL levels in the total patient population at baseline were slightly higher in APOLLO (mean 69.4 pg/mL) than in HELIOS-A (mean 58.2 pg/mL), but did not differ significantly between treatment groups within each study (**Figure 3**)
- Baseline NfL levels in the patient populations of both studies were significantly higher than in healthy controls (p-value <0.001)

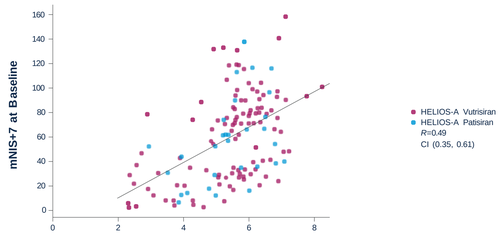
Figure 3. Baseline NfL Levels in APOLLO and HELIOS-A Studies



Association between Baseline mNIS+7 and NfL Levels in HELIOS-A

- In HELIOS-A, a moderate correlation (R=0.49) was observed between mNIS+7 and NfL levels of vutrisiran- and patisiran-treated patients at baseline (**Figure 4**)
  - The strongest correlation was observed with the nerve conduction studies subcomponent of mNIS+7 (R=0.59); other subcomponents showed mild to moderate correlations with NfL levels (data on file)

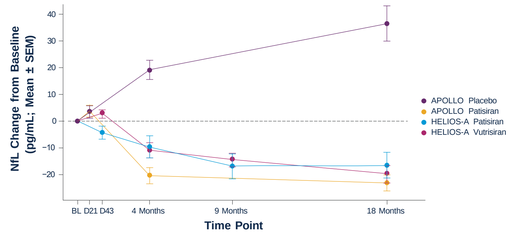
Figure 4. Correlation between Baseline mNIS+7 and NfL Levels in HELIOS-A



NfL Levels Decreased Significantly with TTR RNAi Therapeutics Compared with Placebo

- In APOLLO, NfL levels increased significantly from baseline in the placebo group as early as 4 months (+19.0 pg/mL, p<0.001), and decreased significantly from baseline in the patisiran group at the same time point (−20.4 pg/mL, p<0.001) (**Figure 5**)
- Similarly in HELIOS-A, NfL levels in both the vutrisiran and patisiran groups decreased significantly from baseline by 4 months (vutrisiran, −11.0 pg/mL; patisiran, −9.7 pg/mL; p<0.05)
  - These significant reductions in NfL levels were maintained to 18 months post-treatment initiation relative to baseline (vutrisiran, −19.9 pg/mL; patisiran, −16.4 pg/mL; p<0.01)

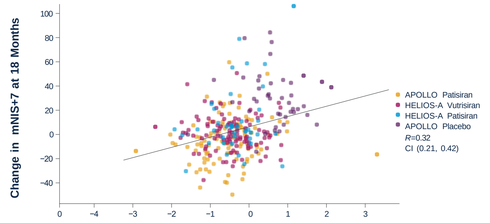
Figure 5. Change in NfL Levels from Baseline in APOLLO and HELIOS-A Studies



Association between Change in mNIS+7 and Change in NfL Levels in APOLLO and HELIOS-A

- A positive moderate correlation (R=0.32) was observed between change in NfL levels and change in mNIS+7 in HELIOS-A and APOLLO at 18 months (**Figure 6**)

Figure 6. Correlation between Change in mNIS+7 and Change in NfL Levels from Baseline in APOLLO and HELIOS-A



Abbreviations: BL, baseline; hATTR, hereditary transthyretin-mediated; IV, intravenous; mNIS+7, modified Neuropathy Impairment Score +7; NfL, neurofilament light chain; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, ribonucleic acid interference; SC, subcutaneous; SEM, standard error of the mean; TTR, transthyretin; wt, wild-type. **References:** 1. Hanna et al. *Curr Heart Fail Rep* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 3. Adams et al. *Neurology* 2015;85:675–82; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Adams et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S14–26; 7. Obici et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S27–35; 8. Adams et al. *Curr Opin Neurol* 2012;25:564–72; 9. Adams et al. *Amyloid* 2012;19(Suppl. 1):61–4; 10. Plante-Bordeneuve et al. *Neurology* 2007;69:693–8; 11. Plante-Bordeneuve et al. *J Med Genet* 2003;40:e120; 12. Mazzeo et al. *J Neuromuscul Dis* 2015;2:S39–48; 13. Alves-Ferreira et al. *Mol Neurobiol* 2018;55:3676–83; 14. Fuchs & Cleveland *Science* 1998;279:514–9; 15. Gunnarsson et al. *Ann Neurol* 2011;69:83–9; 16. Lewczuk et al. *Alzheimers Res Ther* 2018;10:71; 17. Lin et al. *Sci Rep* 2018;8:17368; 18. Byrne et al. *Lancet Neurol* 2017;16:601–9; 19. Bischof et al. *Ann Rheum Dis* 2018;77:1093–4; 20. van Lieverloo et al. *J Peripher Nerv Syst* 2019;24:187–94; 21. Mariotto et al. *J Peripher Nerv Syst* 2018;23:174–7; 22. Sandelius et al. *Neurology* 2018;90:e518–24; 23. Lycke et al. *J Neurol Neurosurg Psychiatry* 1998;64:402–4; 24. Preische et al. *Nat Med* 2019;25:277–83; 25. Louwsma et al. *Amyloid* 2021;28:50–5; 26. Ticau et al. *Neurology* 2021;96:e412–22

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