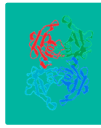
Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION



Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the *transthyretin (TTR)* gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations.[1]

Neurofilament light chain (NfL) is an integral component of the neurons and has been described as a biomarker of neuroaxonal injury across several central and peripheral nervous system diseases, with recent analyses identifying NfL as a potential biomarker of neuronal injury in ATTRv amyloidosis.[3,4]

This analysis evaluated the value of NfL in monitoring treatment response in patients with ATTRv amyloidosis with polyneuropathy whose treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy

NfL for monitoring treatment response in patients with ATTRv

Patient Population
11 patients with confirmed ATTRv amyloidosis with polyneuropathy were included.
Patients had worsening of polyneuropathy of ATTRv amyloidosis with treatment of tafamidis (20mg/day).

Baseline
Assessments:
Serum NfL levels
Neuropathy impairment Score (NIS)

Start patisiran (0.3 mg/kg) IV every three weeks

Month 12 Assessments
Serum NfL levels measured using the Quanterix® Simoa™
Neuropathy Impairment Score

Month 24 Assessments
Serum NfL levels measured using the Quanterix Simoa
Neuropathy Impairment Score

Several effective pharmacological therapies are available, including TTR tetramer stabilizers (diflunisal and tafamidis) and nucleic acid-based medications such as RNA interference therapeutics (patisiran and vutrisiran) and anti-sense oligonucleotide (inotersen).[1,2]

The limitations of this study includes the small number of patients and absence of a control group. Further larger-scale, longer-term studies are necessary to validate the findings.

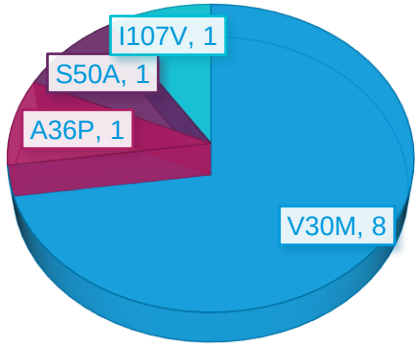
Results

Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg)/day to patisiran (0.3 mg/kg infusion every three weeks).

Patients were switched from tafamidis (20 mg/day) to patisiran due to worsening of polyneuropathy.
All patients included in the study are from a single site in Japan

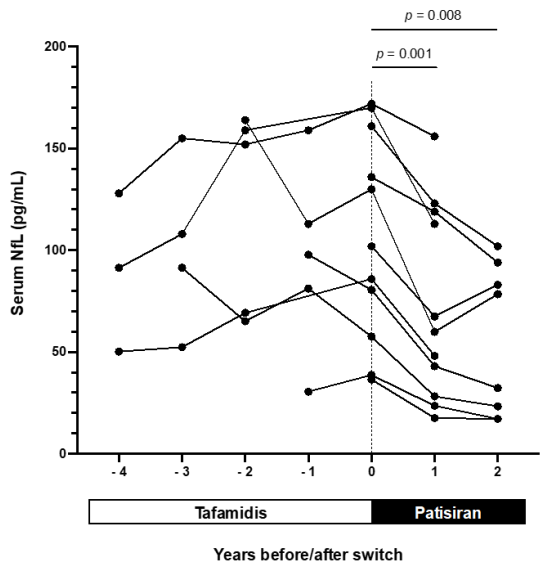
ATTR variants



Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.

Serum NfL levels



Pharmacodynamic Endpoint

Serum NfL levels significantly decreased at one and two years following switch from tafamidis to patisiran . The mean (± SD) NfL level at baseline, before switch, was 106.4 (± 50.7) pg/mL and it decreased to 72.6 (± 47.3) pg/mL one year after switch (p=0.001).

- In patients whose NfL levels were available at two-years post-switch, mean (± SD) value decreased from 92.8 (± 47.0) pg/mL before switch to 55.9 (± 36.7) pg/mL following two years of patisiran treatment (p=0.008).

Neurologic Impairment Endpoint

- No significant change was observed in NIS values at one -and-two years following switch. The mean (±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at one year after switch to patisiran treatment (*p*=0.180).
- In the patients with two-year assessment, the values before and two years after switch were 47.8 (±49.6) and 55.4 (±51.0), respectively (*p*=0.547).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Author Conclusions: The results show that treatment switch from tafamidis to patisiran may significantly decrease serum NfL levels at one and two years.

MED-US-TTR02-2300015 | March 13, 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the *transthyretin (TTR)* gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations

Neurofilament light chain (NfL) is an integral component of the neurons and has been described as a biomarker of neuroaxonal central and peripheral nervous system diseases, identifing NfL as a potential biomarker of neuronal amyloidosis

In this analysis, we evaluated the value of NfL in response in patients with ATTRv amyloidosis with treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy

NfL for monitoring treatment response in patients with ATTRv

- **Patient Population**
  11 patients with confirmed ATTRv amyloidosis with polyneuropathy

Baseline: Mean age at disease onset 39.5 years; Mean age at inclusion was 46.9 years

patisiran (0.3 mg/kg)

Month 12: Serum NfL levels Quanterix Simoa; NIS assessment

Month 24: Serum NfL levels (Quanterix Simoa); NIS assessment

of this study included its small number of patients and ontrol group. Further larger-scale, longer-term studies are alidate our findings.

Author Information

Mitsuto Sato[1], Yusuke Mochizuki[1], Yusuke Takahashi[1], Ken Takasone[1], Emre Aldinc[2], Simina Ticau[2], Gang Jia[2], Yoshiki Sekijima[1,3]

[1]Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Nagano, Japan

[2]Alnylam Pharmaceuticals, Cambridge, MA, USA

[3]Institute for Biomedical Sciences, Shinshu University, Nagano, Japan

Abbreviations

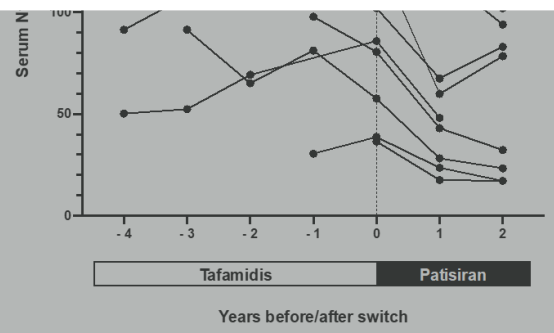
Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.

Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ts

nge was observed in NIS values at one -and-two years following ±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch and 55.4 (±51.0), respectively (p=0.547).

c Endpoints

cantly decreased at one and two years following switch from tafamidis to patisiran . The mean (□SD) NfL level at baseline, before switch, was 106.4 (□50.7) pg/mL and it decreased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).

- In patients whose NfL levels were available at two-years post-switch, mean (□SD) value decreased from 92.8 (□47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two years of patisiran treatment (p=0.008).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

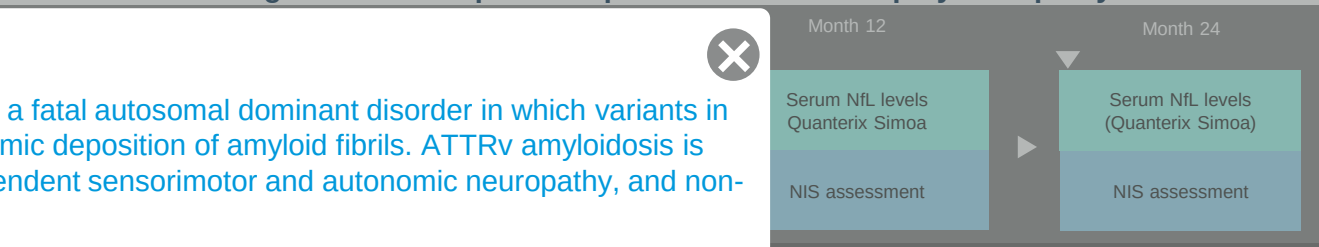
INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosc
which variants in the *transthyretin (TTR)* gene cause sys
fibrils. ATTRv amyloidosis is characterized by progress
sensorimotor and autonomic neuropathy, and non-neurop

Neurofilament light chain (NfL) is an integral compo
has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, w
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy



of this study included its small number of patients and
ontrol group. Further larger-scale, longer-term studies are
alidate our findings.

INTRODUCTION

- Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the transthyretin (TTR) gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations.[1]
- Several effective pharmacological therapies are available, including TTR tetramer stabilizers (diflunisal and tafamidis) and nucleic acid-based medications such as RNA interference therapeutics (patisiran and vutrisiran) and anti-sense oligonucleotide (inotersen).[1,2] However, evaluation and monitoring of disease progression and treatment response are challenging in clinical practice, because existing assessment methods are not sensitive enough to detect changes in disease activity.
- Neurofilament light chain (NfL) is an integral component of the neurons, and has been described as a biomarker of neuroaxonal injury across several central and peripheral nervous system diseases, with recent analyses identifing NfL as a potential biomarker of neuronal injury in ATTRv amyloidosis.[3,4]
- This analysis, we evaluated the value of NfL in monitoring treatment response in patients with ATTRv amyloidosis with polyneuropathy whose treatment was switched from tafamidis to patisiran.

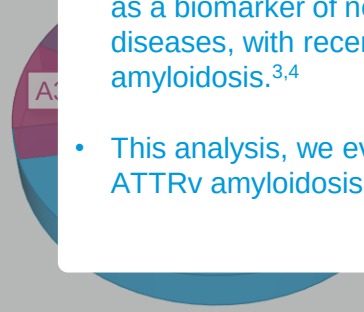
Abbreviations

Results

Patients

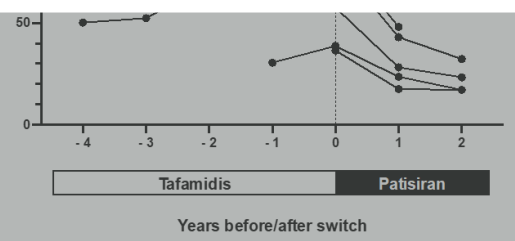
This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.



Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ts

ge was observed in NIS values at one -and-two years following
(±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at
ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch
and 55.4 (±51.0), respectively (p=0.547).

ic Endpoints

cantly decreased at one and two years following switch from
The mean (□SD) NfL level at baseline, before switch, was 106.4
creased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).
evels were available at two-years post-switch, mean (□SD) value
47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two
years of patisiran treatment (p=0.008).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

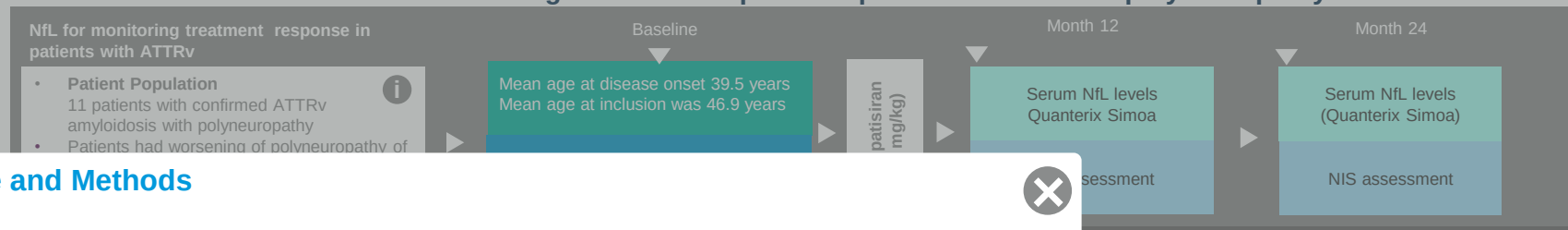
INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the *transthyretin (TTR)* gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations

Neurofilament light chain (NfL) is an integral component of the neurons, and has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, w
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy



udy included its small number of patients and up. Further larger-scale, longer-term studies are r findings.

Study Rationale and Methods

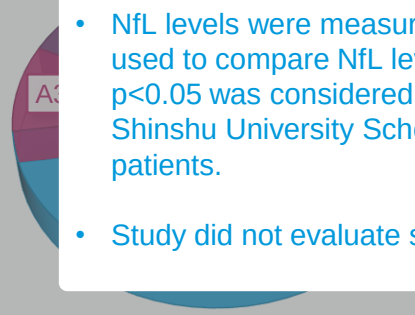
- This analysis, we evaluated the value of NfL in monitoring treatment response in patients with ATTRv amyloidosis with polyneuropathy whose treatment was switched from tafamidis to patisiran.
- Serum NfL levels of patients were measured at baseline (while receiving tafamidis, just before switch), one and two years after switch to patisiran.
- Patients were also assessed for neurologic impairment with neuropathy impairment score (NIS) at baseline and one and/or two years following switch.
- NfL levels were measured using the Quanterix® Simoa™ platform. The Wilcoxon signed-rank test was used to compare NfL levels and NIS values before, and one and two years after switch to patisiran. p<0.05 was considered statistically significant. This study was approved by the Ethical Committee of Shinshu University School of Medicine (No. 4852) and written informed consent was obtained from patients.
- Study did not evaluate safety.

Abbreviations

Patients

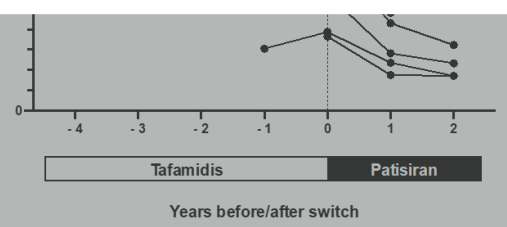
This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.



Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



bserved in NIS values at one -and-two years following values were 40.4 (±43.7) before switch and 46.3 (±49.6) at iran treatment (p=0.180).
assessment, the values before and two years after switch ±51.0), respectively (p=0.547).

oints
eased at one and two years following switch from SD) NfL level at baseline, before switch, was 106.4 72.6 (47.3) pg/mL one year after switch (p=0.001).
available at two-years post-switch, mean (SD) value L before switch to 55.9 (36.7) pg/mL following two 08).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

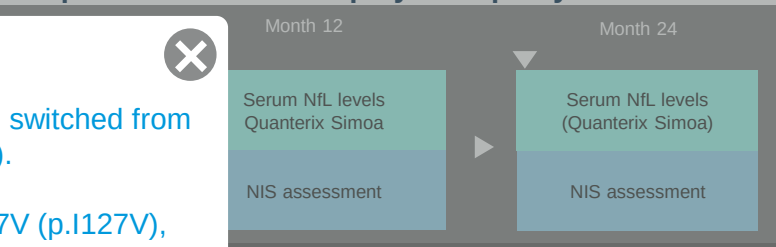
INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosc
which variants in the *transthyretin (TTR)* gene cause sys
fibrils. ATTRv amyloidosis is characterized by progressi
sensorimotor and autonomic neuropathy, and non-neurop

Neurofilament light chain (NfL) is an integral compo
has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, wi
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy

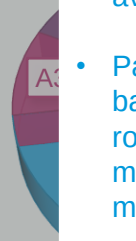


of this study included its small number of patients and
ontrol group. Further larger-scale, longer-term studies are
alidate our findings.

Patients

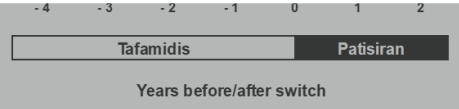
This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.



Mean (±SD)
were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ts

nge was observed in NIS values at one -and-two years following
±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at
ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch
and 55.4 (±51.0), respectively (p=0.547).

c Endpoints

cantly decreased at one and two years following switch from
he mean (□SD) NfL level at baseline, before switch, was 106.4
creased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).
evels were available at two-years post-switch, mean (□SD) value
47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two
ent (p=0.008).

om tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.

- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Patient Population

- This study enrolled eleven patients (10 male) with ATTRv with polyneuropathy who switched from tafamidis (20mg oral once daily) to patisiran (0.3 mg/kg infusion every three weeks).
- TTR variants were V30M (p.V50M) (n=8), A36P (p.A56P), S50A (p.S70A), and I107V (p.I127V), (n=1 each).
  - Mean (±SD) age at disease onset 39.5 years ± 12.6 years
  - Mean (±SD) age at inclusion was 46.9 years ± 14.0 years
- The reason for switch from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks was due to worsening of polyneuropathy.
- Serum NfL levels of patients were measured at baseline (while receiving tafamidis, just before switch), one and two years after switch to patisiran. In eight of the eleven patients, NfL levels were available at two years following switch.
- Patients were also assessed for neurologic impairment with neuropathy impairment score (NIS) at baseline and one and/or two years following switch. Since the patients were assessed during routine visits, NfL and NIS measurements at 1-year and 2-year post-switch occurred within 3 months of those time points, except one patient whose 2-year measurements were delayed by four months.

Abbreviations

Results

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUC

Hereditary ATTR (ATTRv) amyloidosis is a
which variants in the *transthyretin (TTR)* ge
fibrils. ATTRv amyloidosis is characterized
sensorimotor and autonomic neuropathy, and

Neurofilament light chain (NfL) is an inte
has been described as a biomarker of ne
central and peripheral nervous system d
identifing NfL as a potential biomarker of
amyloidosis

In this analysis, we evaluated the value
response in patients with ATTRv amyloid
treatment was switched from tafamidis to

RESULTS

- Serum NfL levels significantly decreased at one and two years following switch from tafamidis to patisiran. The mean (±SD) NfL level at baseline, before switch, was 106.4 (±50.7) pg/mL and it decreased to 72.6 (±47.3) pg/mL one year after switch (p=0.001). In patients whose NfL levels were available at two-years post-switch, mean (±SD) value decreased from 92.8 (±47.0) pg/mL before switch to 55.9 (±36.7) pg/mL following two years of patisiran treatment (p=0.008). Additionally, NfL levels increased while on tafamidis in more than half of seven patients with NfL measurements available from before switch.
- No significant change was observed in NIS values at one and two years following switch. The mean (±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at one year after switch to patisiran treatment (p=0.180). In the patients with two-year assessment, the values before and two years after switch were 47.8 (±49.6) and 55.4 (±51.0), respectively (p=0.547).
- This analysis evaluated the value of NfL in monitoring treatment response in patients with ATTRv amyloidosis with polyneuropathy whose treatment was switched from tafamidis to patisiran.
- The results showed treatment switch from tafamidis to patisiran may significantly decrease serum NfL levels at one and two years. These results are consistent with the significant decrease in NfL levels with patisiran reported in a similar patient population from APOLLO trial. Decreased NfL levels and stable NIS after switch from tafamidis to patisiran suggests attenuation of active neuronal damage by patisiran.
- The limitations of this study included its small number of patients and absence of a control group. Further larger-scale, longer-term studies are necessary to validate the findings.

Abbreviations

olyneuropathy

Month 24

els
oa
nt

Serum NfL levels (Quanterix Simoa)

NIS assessment

uded its small number of patients and
ther larger-scale, longer-term studies are
gs.

Results

Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.

in NIS values at one -and-two years following
were 40.4 (±43.7) before switch and 46.3 (±49.6) at
tment (p=0.180).
ent, the values before and two years after switch
respectively (p=0.547).

t one and two years following switch from
L level at baseline, before switch, was 106.4
47.3) pg/mL one year after switch (p=0.001).
e at two-years post-switch, mean (□SD) value
switch to 55.9 (□36.7) pg/mL following two

Tafamidis | Patisiran

Years before/after switch

patisiran significantly decreased serum NfL
oidosis with polyneuropathy.

- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autoso
which variants in the *transthyretin (TTR)* gene cause sys
fibrils. ATTRv amyloidosis is characterized by progressi
sensorimotor and autonomic neuropathy, and non-neurop

Neurofilament light chain (NfL) is an integral compo
has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, wi
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Results

Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

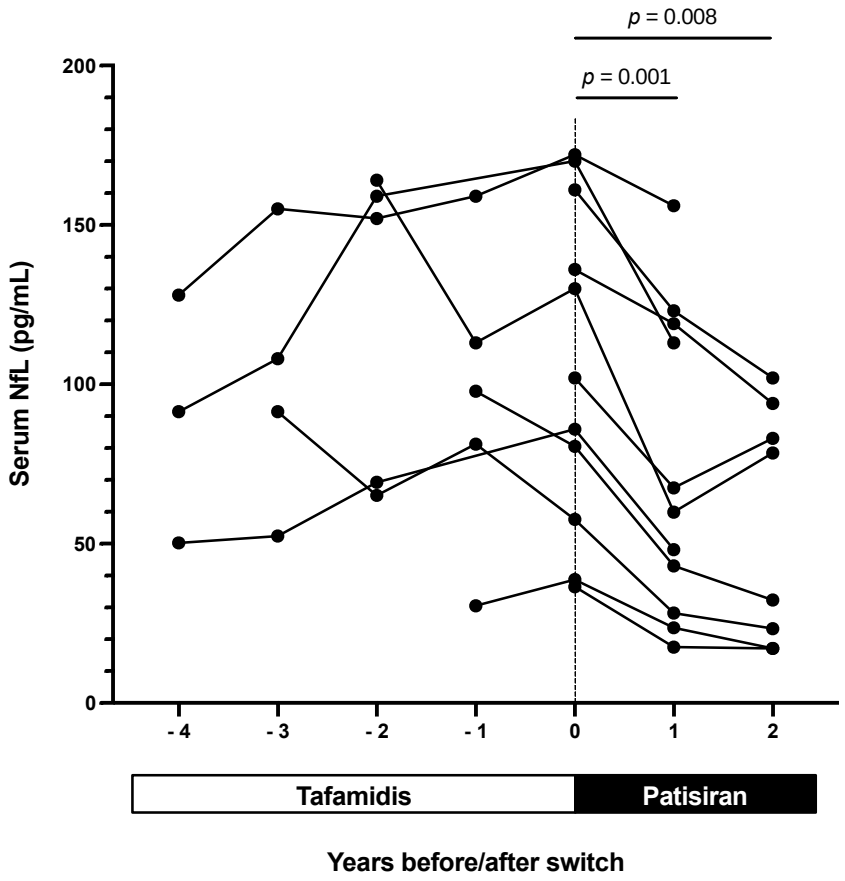
Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.

Mean (±SD)
were 39.5±1

Serum NfL l
patients at o
respectively.

Years before/after switch

Figure 1



Serum NfL levels before and after switch from tafamidis to patisiran. Pre-switch NfL levels are depicted according to the calendar year in which the measurement was made.

Abbreviations

ATTRv polyneuropathy

Month 12 | Month 24

Serum NfL levels (Quanterix Simoa) | Serum NfL levels (Quanterix Simoa)

NIS assessment | NIS assessment

this study included its small number of patients and rol group. Further larger-scale, longer-term studies are late our findings.

was observed in NIS values at one -and-two years following D) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at o patisiran treatment (p=0.180).
o-year assessment, the values before and two years after switch 55.4 (±51.0), respectively (p=0.547).

Endpoints

tly decreased at one and two years following switch from mean (□SD) NfL level at baseline, before switch, was 106.4 ased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).
s were available at two-years post-switch, mean (□SD) value 0) pg/mL before switch to 55.9 (□36.7) pg/mL following two t (p=0.008).

tafamidis to patisiran significantly decreased serum NfL ATTRv amyloidosis with polyneuropathy.

in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

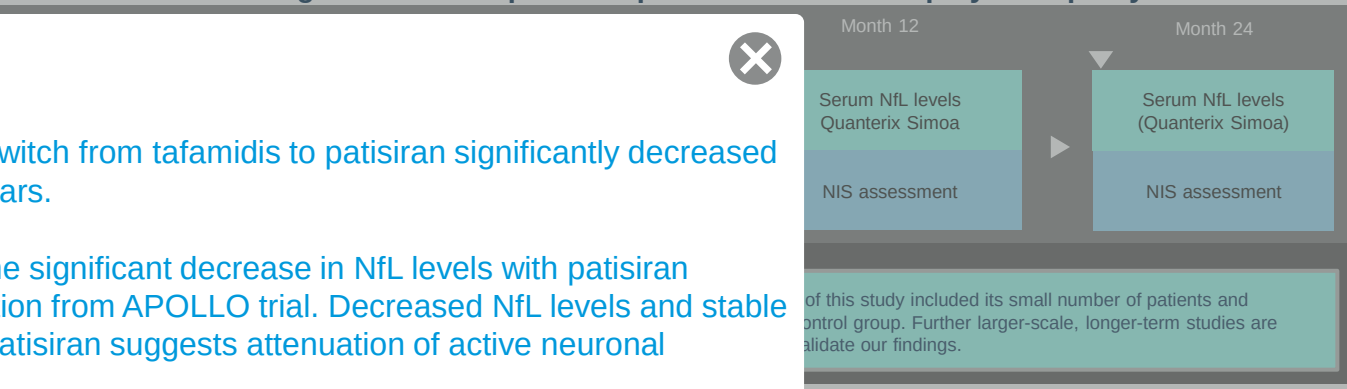
INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosc
which variants in the *transthyretin (TTR)* gene cause sys
fibrils. ATTRv amyloidosis is characterized by progressi
sensorimotor and autonomic neuropathy, and non-neurop

Neurofilament light chain (NfL) is an integral compo
has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, wi
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy



of this study included its small number of patients and
ontrol group. Further larger-scale, longer-term studies are
alidate our findings.

Author Conclusions

- This study showed that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.
- These results are consistent with the significant decrease in NfL levels with patisiran reported in a similar patient population from APOLLO trial. Decreased NfL levels and stable NIS after switch from tafamidis to patisiran suggests attenuation of active neuronal damage by patisiran.
- The limitations of this study included its small number of patients and absence of a control group. Further larger-scale, longer-term studies are necessary to validate the findings.

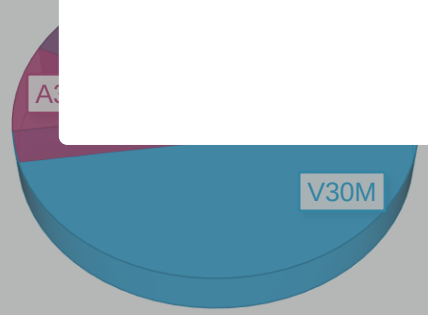
Abbreviations

Results

Patients

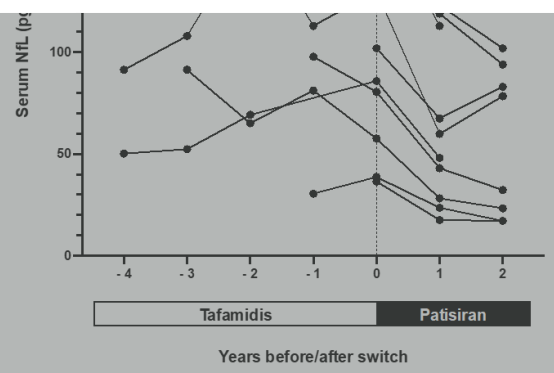
This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.



Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ts

ge was observed in NIS values at one -and-two years following
±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at
ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch
and 55.4 (±51.0), respectively (p=0.547).

Pharmacodynamic Endpoints

Abbreviations

- Serum NfL levels significantly decreased at one and two years following switch from tafamidis to patisiran . The mean (□SD) NfL level at baseline, before switch, was 106.4 (□50.7) pg/mL and it decreased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).
- In patients whose NfL levels were available at two-years post-switch, mean (□SD) value decreased from 92.8 (□47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two years of patisiran treatment (p=0.008).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Abbreviations

ATTR, transthyretin mediated

ATTRv amyloidosis, hereditary ATTR amyloidosis

IV, intravenous

NfL, neurofilament light chain

NIS, Neuropathy impairment score

RNAi, RNA interference

SD, standard deviation

TTR, transthyretin

INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the *transthyretin (TTR)* gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations

Neurofilament light chain (NfL) is an integral component of the neurons, and has been described as a biomarker of neuroaxonal
central and peripheral nervous system diseases, w
identifing NfL as a potential biomarker of neuronal i
amyloidosis

In this analysis, we evaluated the value of NfL in m
response in patients with ATTRv amyloidosis with p
treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy

of this study included its small number of patients and
ontrol group. Further larger-scale, longer-term studies are
alidate our findings.

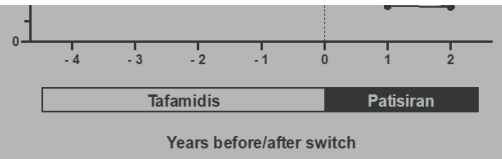
Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.

Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ts

nge was observed in NIS values at one -and-two years following
(±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at
ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch
and 55.4 (±51.0), respectively (p=0.547).

ic Endpoints

cantly decreased at one and two years following switch from
The mean (□SD) NfL level at baseline, before switch, was 106.4
creased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).
evels were available at two-years post-switch, mean (□SD) value
47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two
ment (p=0.008).

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |

Abbreviations

Neurofilament light chain as a biomarker for monitoring response to change in treatment in hereditary ATTR amyloidosis

Sato et al. *Amyloid* 2023. Sponsored and funded by Alnylam Pharmaceuticals.

Study Design

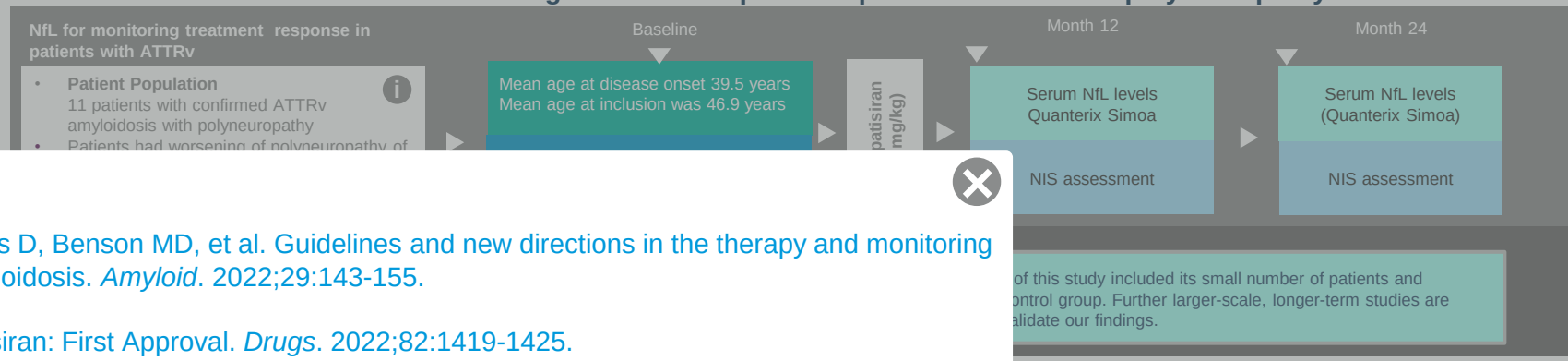
INTRODUCTION

Hereditary ATTR (ATTRv) amyloidosis is a fatal autosomal dominant disorder in which variants in the *transthyretin (TTR)* gene cause systemic deposition of amyloid fibrils. ATTRv amyloidosis is characterized by progressive length-dependent sensorimotor and autonomic neuropathy, and non-neuropathic manifestations

Neurofilament light chain (NfL) is an integral component of the neurons, and has been described as a biomarker of neuroaxonal central and peripheral nervous system diseases, w identifing NfL as a potential biomarker of neuronal i amyloidosis

In this analysis, we evaluated the value of NfL in m response in patients with ATTRv amyloidosis with p treatment was switched from tafamidis to patisiran.

Serum NfL for monitoring treatment response in patients with ATTRv polyneuropathy



of this study included its small number of patients and ontrol group. Further larger-scale, longer-term studies are alidate our findings.

References

1. Ando Y, Adams D, Benson MD, et al. Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis. *Amyloid*. 2022;29:143-155.

2. Keam SJ. Vutrisiran: First Approval. *Drugs*. 2022;82:1419-1425.

3. Ticau S, Sridharan GV, Tsour S, et al. Neurofilament light chain as a biomarker of hereditary transthyretin-mediated amyloidosis. *Neurology*. 2021;96:e412-e422.

4. Maia LF, Maceski A, Conceição I, et al. Plasma neurofilament light chain: an early biomarker for hereditary ATTR amyloid polyneuropathy. *Amyloid*. 2020;27:97-102.

5. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79:785-792.

Abbreviations

Results

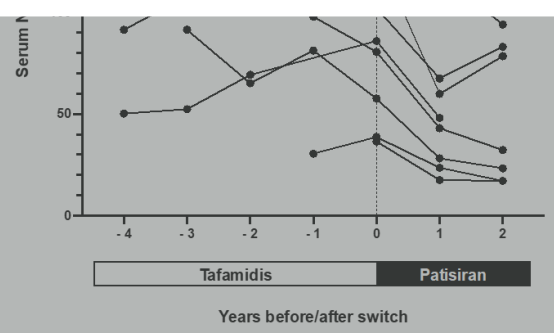
Patients

This study enrolled eleven patients with ATTRv with polyneuropathy who switched from tafamidis (20mg) to patisiran (0.3 mg/kg infusion every three weeks)

Patients were switched from tafamidis (20 mg) to patisiran (0.3 mg/kg infusion every three weeks due to worsening of polyneuropathy.

Mean (±SD) age at disease onset and study inclusion were 39.5±12.6 and 46.9±14.0 years, respectively.

Serum NfL levels were available for 11/11 and 8/11 patients at one and two-years following switch, respectively.



ge was observed in NIS values at one -and-two years following ±SD) NIS values were 40.4 (±43.7) before switch and 46.3 (±49.6) at ch to patisiran treatment (p=0.180).
two-year assessment, the values before and two years after switch and 55.4 (±51.0), respectively (p=0.547).

c Endpoints

cantly decreased at one and two years following switch from tafamidis to patisiran . The mean (□SD) NfL level at baseline, before switch, was 106.4 (□50.7) pg/mL and it decreased to 72.6 (□47.3) pg/mL one year after switch (p=0.001).

- In patients whose NfL levels were available at two-years post-switch, mean (□SD) value decreased from 92.8 (□47.0) pg/mL before switch to 55.9 (□36.7) pg/mL following two years of patisiran treatment (p=0.008).

Summary

- Treatment switch from tafamidis to patisiran significantly decreased serum NfL levels in patients with ATTRv amyloidosis with polyneuropathy.
- The observed decrease in NfL levels, together with stable NIS following switch from tafamidis suggests attenuation of active neuronal damage by patisiran treatment.

Conclusions: Our study demonstrated that treatment switch from tafamidis to patisiran significantly decreased serum NfL levels at one and two years.

MED-US-TTR02-2300015 | April 2023 |