Effectiveness of Patisiran Following Switch From Tafamidis for the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with Polyneuropathy

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Introduction

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, rapidly progressive, debilitating, and fatal disease caused by variants in the transthyretin (*TTR*) gene[1–4]
  - The majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[5,6]
- Polyneuropathy can manifest as sensory, autonomic, and motor neuropathy[2,6–13]
- Disease progression can lead to significant disability, decreased health-related quality of life, loss of physical function, and death[14,15]

Tafamidis

- A small-molecule TTR stabilizer shown to slow neuropathy progression and maintain the quality of life in the per-protocol population of the pivotal FX-005 study of patients with V30M hATTR amyloidosis with early-stage polyneuropathy; tafamidis has been approved in select jurisdictions, including the EU[16–18] **(Figure 1)**

Patisiran

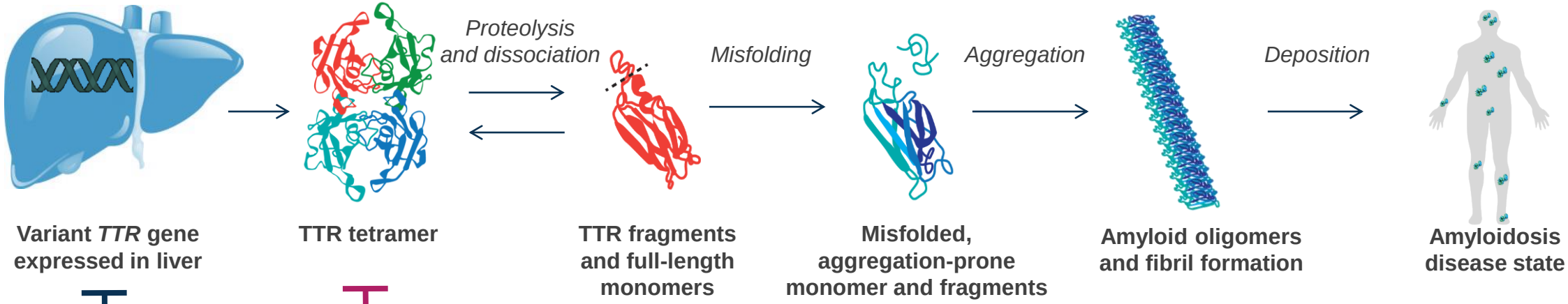
- An RNAi therapeutic shown to halt or reverse polyneuropathy and improve quality of life in the pivotal APOLLO study of patients with hATTR amyloidosis with a wide range of polyneuropathy severity; patisiran has been approved in multiple jurisdictions, including the EU[19–21] **(Figure 1)**

Abbreviations: ATTRv, hereditary transthyretin (v for variant); EU, European Union; hATTR, hereditary transthyretin mediated; RNAi, RNA interference; TTR, transthyretin.

References: 1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Hawkins et al. *Ann Med* 2015;47:625–38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 5. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 6. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 7. Ando et al. *Orphanet J Rare Dis* 2013;8:31; 8. Živković et al. *Amyloid* 2020;27:142–3; 9. Visser & Klein. *Neurology* 2017;88:1101–2; 10. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 11. Shin & Robinson-Papp. *Mt Sinai J Med* 2012;79:733–48; 12. Gonzalez-Duarte. *Clin Auton Res* 2019;29:245–51; 13. Wixner et al. *Orphanet J Rare Dis* 2014;9:61; 14. Adams et al. *Neurology* 2015; 85:675–82; 15. Adams et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S14–26; 16. Coelho et al. *Neurology* 2012;79:785–92; 17. European Medicines Agency. Summary of product characteristics: Vyndaqel 20 mg soft capsules. Available from: https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf (accessed May 2022); 18. Waddington Cruz & Benson. *Neurol Ther* 2015;4:61–79; 19. Coelho et al. *N Engl J Med* 2013;369:819–29; 20. Adams et al. *N Engl J Med* 2018;379:11–21; 21. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed May 2022)

Introduction

Figure 1. Disease Cascade



Tafamidis

Binds and stabilizes the TTR tetramer

Phase 3 pivotal study (**FX-005**) population characteristics:
- 100% V30M variant
- 100% FAP Stage 1

EMA Indication: Stage 1 polyneuropathy

Patisiran

Reduces production of both variant and wt TTR mRNA

Phase 3 pivotal study (APOLLO) population characteristics:
- 39 different *TTR* variants
- 46% FAP Stage I, 53% FAP Stage 2

EMA Indication: Stage 1 or 2 polyneuropathy

Study Objectives:
- Describe the clinical rationale for treatment switch from tafamidis to patisiran in patients with hATTR amyloidosis with polyneuropathy
- Evaluate the effectiveness of tafamidis prior to treatment switch and the effectiveness of patisiran in the 12-month post-switch period

Abbreviations: EMA, European Medicines Agency; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin mediated; mRNA, messenger RNA; TTR, transthyretin; wt, wild type.

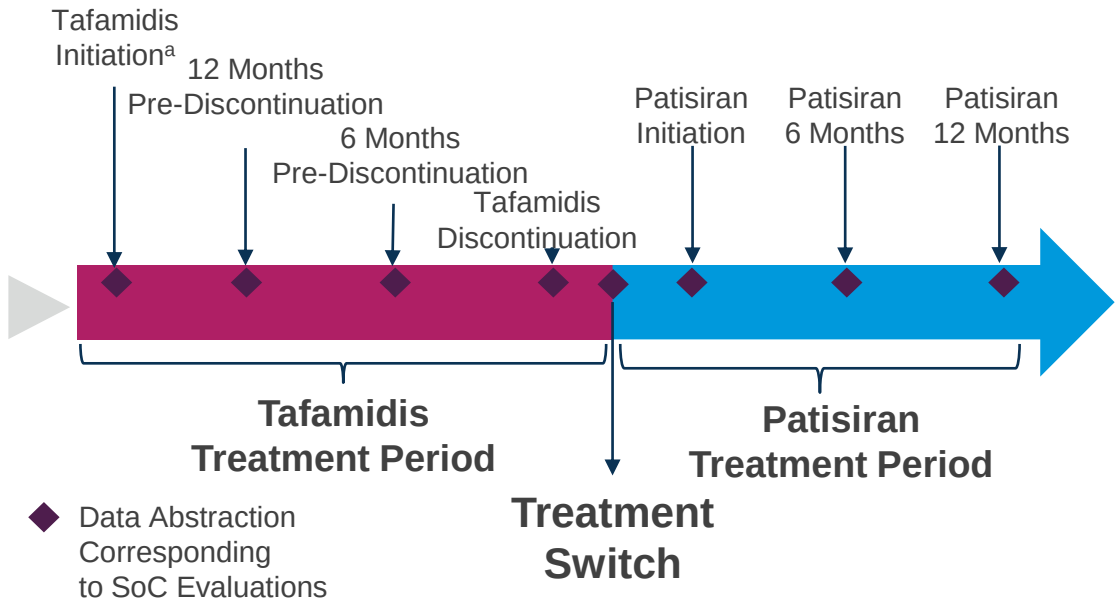
Methods

- This was a retrospective, single-center, observational chart review study at a large expert referral center in France (**Figure 2**)
- Data were extracted from medical charts of eligible patients with hATTR amyloidosis with polyneuropathy treated in the Centre Hospitalier Universitaire Bicêtre who switched from tafamidis to patisiran on or prior to August 30, 2019
  - Data elements extracted included patient demographics, treatment, and disease measures during tafamidis treatment, rationale for treatment switch from tafamidis to patisiran, and real-world outcomes during the first 12 months of patisiran treatment
  - All data elements were extracted from medical records based on clinical assessments at routine visits, per the site's standard of care

Figure 2. Study Design

Key Selection Criteria

- Confirmed diagnosis of hATTR amyloidosis with documented *TTR* variant
- Documented initiation and discontinuation of tafamidis for the treatment of hATTR amyloidosis with PN prior to initiation of patisiran
- Stage 1 or 2 PN at the initiation of patisiran



Key Endpoints Assessed[b]

Clinical rationale for treatment switch:
- Disease progression due to new-onset/worsening polyneuropathy or cardiomyopathy
- Other reasons

Selected effectiveness measurements during tafamidis and patisiran treatment periods:
- PND score
- Walking difficulties
- NIS

[a]If data from tafamidis treatment initiation were unavailable, data from the first clinical visit available at the center during the tafamidis treatment period were abstracted. [b]All data were collected per the site's standard of care. Additional measures to assess progression and treatment effectiveness included, but were not limited to, manual grip strength, BMI, diarrhea severity, orthostatic intolerance severity, nerve conduction studies, and erectile dysfunction severity.

Abbreviations: BMI, body mass index; hATTR, hereditary transthyretin mediated; NIS, Neuropathy Impairment Score; PN, polyneuropathy; PND, Polyneuropathy Disability; SoC, standard of care; TTR, transthyretin.

Results

Patient Demographics and Disease Characteristics

- With the exception of 1 patient, the population consisted of late-onset V30M and non-V30M hATTR amyloidosis (**Table 1**)

Table 1. Patient Characteristics at Time of Patisiran Initiation

Characteristic	n=24
Age at the initiation of patisiran, years, mean (SD) [min, max]	67.29 (7.98) [40.00, 76.00]
Male sex, n (%)	16 (66.67)
Mutation type, n (%)	24 (100.00)
Early-onset V30M (≤50 years of age at onset)	1 (4.17)
Late-onset V30M (>50 years of age at onset)	11 (45.83)
Non-V30M[a]	12 (50.00)
Select comorbidities at the initiation of patisiran, n (%)	
Heart arrhythmia/conduction disturbance	7 (29.17)
Related to hATTR amyloidosis	4 (57.14)
Timing of key study milestones, months, mean (SD)	
Duration of hATTR amyloidosis at the initiation of patisiran	34.12 (18.44)
Duration of tafamidis use at the initiation of patisiran	30.05 (17.53)
Duration between discontinuation of tafamidis and initiation of patisiran	0.34 (1.12)
Duration of patisiran use during follow-up (up to 12 months)	11.72 (1.35)

[a]Non-V30M mutation types included: S77Y (n=6), I107V (n=2), T69I (n=1), T59R (n=1), T49A (n=1), and T60A (n=1)

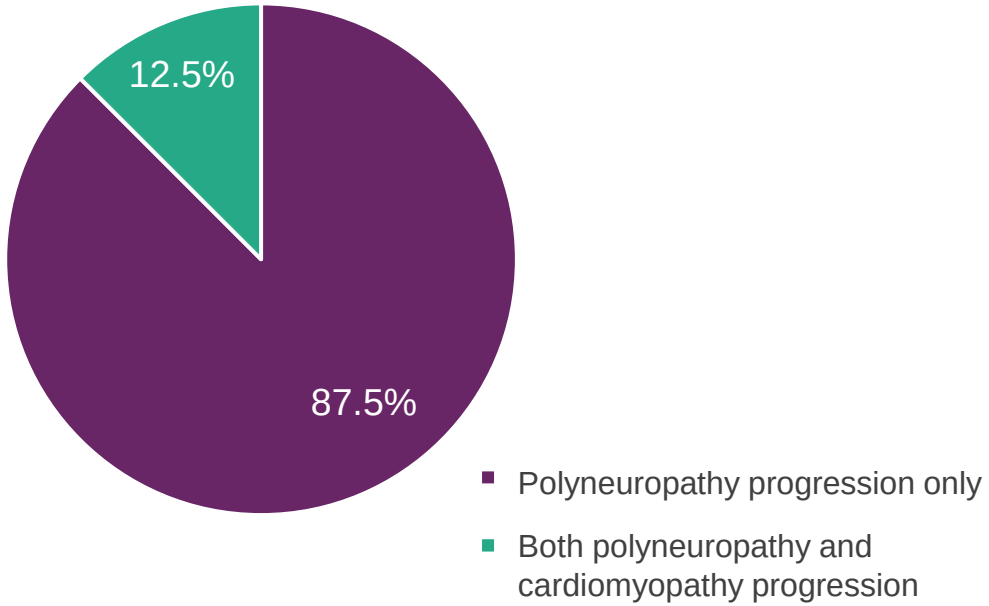
Abbreviations: hATTR, hereditary transthyretin mediated; SD, standard deviation.

Results

Reasons for Switch from Tafamidis to Patisiran (1)

- All 24 patients discontinued tafamidis and switched to patisiran due to neuropathic disease progression (**Figure 3**)
  - 3 (12.5%) patients discontinued tafamidis and switched to patisiran due to progression in both neuropathy and cardiomyopathy

Figure 3. Reasons for Discontinuing Tafamidis to Initiate Patisiran

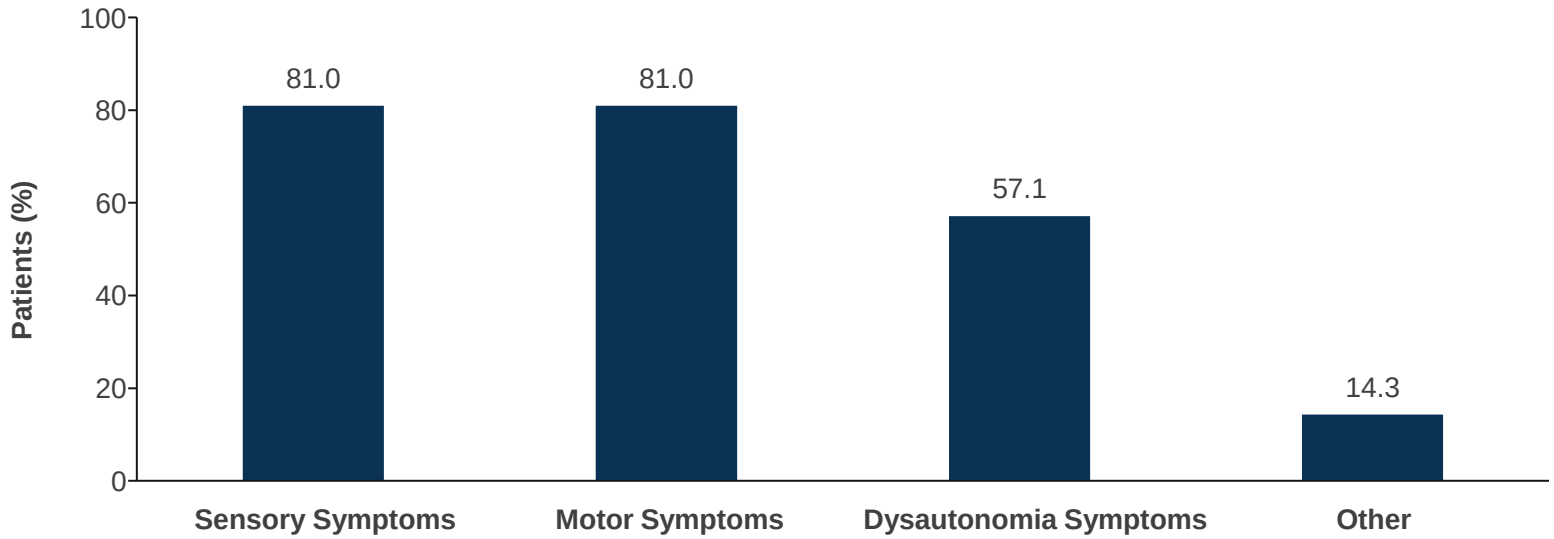


Results

Reasons for Switch from Tafamidis to Patisiran (2)

- Patient-reported worsening neuropathy symptoms informed the clinical rationale to switch in 21 (87.5%) patients (**Figure 4**)

Figure 4. New/Worsening Neuropathy Symptoms Informing the Clinical Rationale to Switch hATTR Amyloidosis Therapy[a,b] (n=21)



Other: reduction of walking distance, new lipothymia, and new hand gesture disability

[a]New/worsening symptoms were based on the patient's subjective report of disease symptoms; clinical signs were objective measures based on the physician's clinical examination. [b]The data categories in each bar chart are not mutually exclusive and some patients could have switched for >1 reason

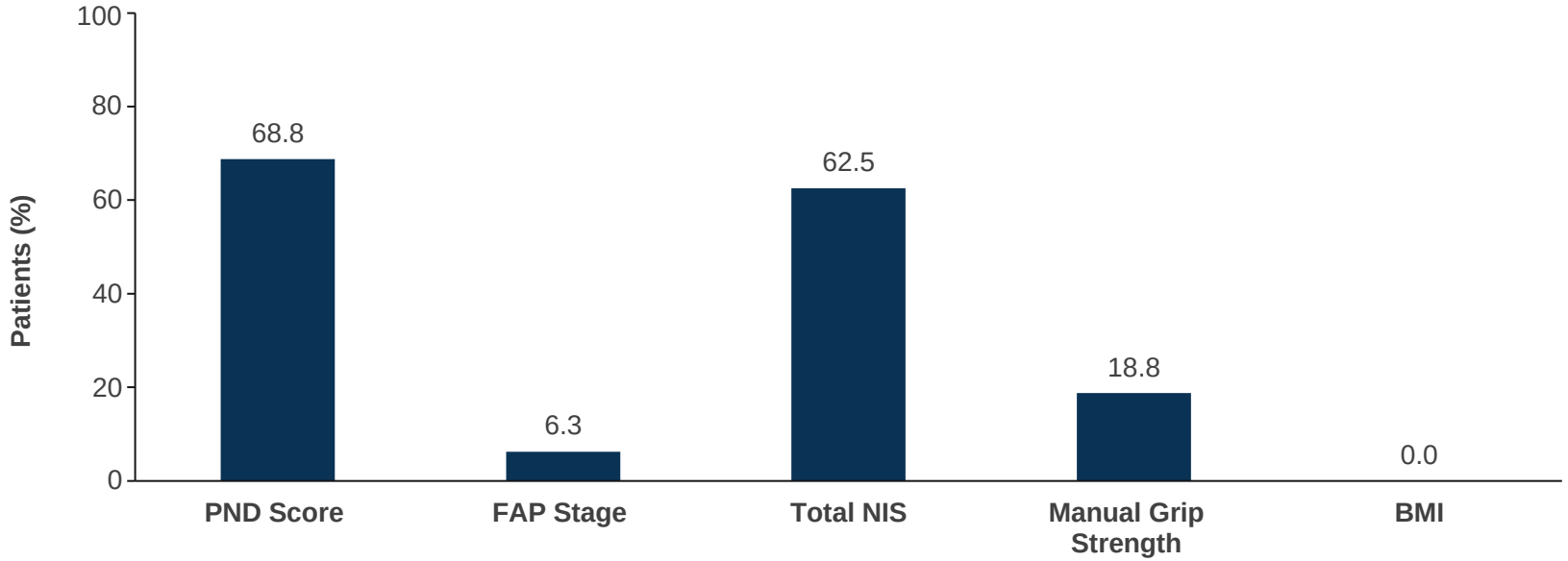
Abbreviations: hATTR, hereditary transthyretin mediated.

Results

Reasons for Switch from Tafamidis to Patisiran (3)

- Objective neuropathy signs measured by the clinician informed the rationale to switch in 16 (66.7%) patients (**Figure 5**)

Figure 5. Worsening Neuropathy Clinical Signs Informing the Clinical Rationale to Switch hATTR Amyloidosis Therapy[a,b] (n=16)



[a]New/worsening symptoms were based on the patient's subjective report of disease symptoms; clinical signs were objective measures based on the physician's clinical examination. [b]The data categories in each bar chart are not mutually exclusive and some patients could have switched for >1 reason

Abbreviations: BMI, body mass index; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin mediated; NIS, Neuropathy Impairment Score; PND, Polyneuropathy Disability.

Results

Neuropathy Impairment (NIS) During Tafamidis and Patisiran Treatment

- Over the tafamidis treatment period (mean duration 30.05 months), mean (SD) change in NIS was +24.87 [17.08], indicating worsening of neuropathy (**Table 2**)
- Following switch to patisiran, mean (SD) change in NIS began to stabilize compared with patisiran treatment baseline (change from patisiran initiation to Month 6: +5.00 [13.45], to Month 12: +2.36 [12.76]) (**Table 2**)
  - However, mean (SD) NIS did not return to levels observed at initiation of tafamidis

Table 2. NIS During Tafamidis and Patisiran Treatment

Neuropathy Impairment (NIS)[a]	Initiation of Tafamidis	12 months Prior to Discontinuation of Tafamidis	6 months Prior to Discontinuation of Tafamidis	Discontinuation of Tafamidis[e]	Initiation of Patisiran[e]	6 months After Initiation of Patisiran	12 months After Initiation of Patisiran
Number of patients assessed	24	14	13	23	23	19	15
Total NIS, mean (SD)	**36.92** (17.29)	**53.36** (16.62)	**58.62** (21.10)	**61.70** (19.97)	**61.70** (19.97)	**64.95** (21.50)	**59.13** (22.71)
Change in NIS, mean (SD)[b,c,d]	—	**+17.00** (18.38)	**+21.31** (19.66)	**+24.87** (17.08)	—	**+5.00** (13.45)	**+2.36** (12.76)

[a]NIS is graded on a scale of 0–244, with higher score indicating worse impairment. [b]Change in NIS at visits associated with tafamidis treatment is calculated as the difference from NIS at tafamidis initiation. [c]Change in NIS at visits associated with patisiran treatment is calculated as the difference from NIS at patisiran initiation. [d]Change in NIS is assessed for patients who had non-missing NIS at both standard of care visits. [e]In instances where data were not available from 2 distinct standard of care evaluations and treatment decisions occurred simultaneously as part of the same visit, the measures from the visit were included under both milestones. For 2 patients, the tafamidis discontinuation SoC visit was not reported but the discontinuation occurred < 36 days before the initiation of patisiran. For these 2 patients the measures from the patisiran initiation visit were included under both milestones

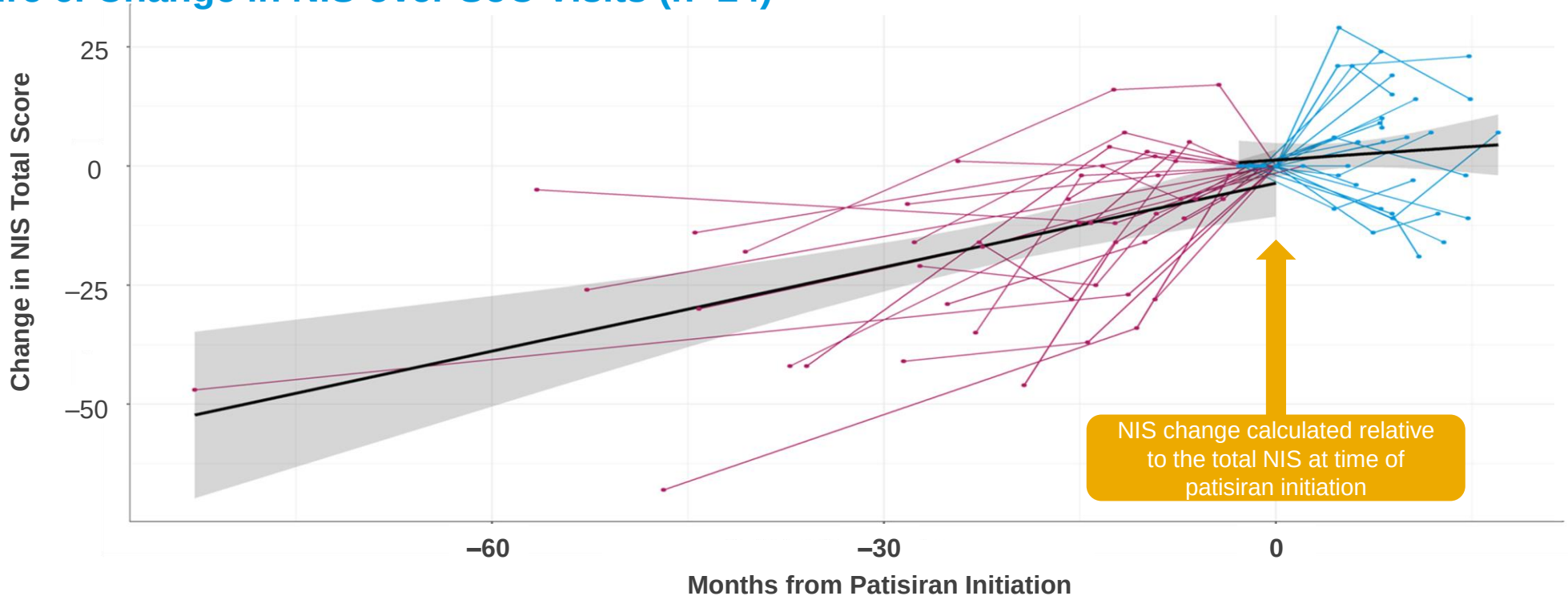
Abbreviations: NIS, Neuropathy Impairment Score; SD, standard deviation; SoC, standard of care.

Results

Change in NIS over SoC Visits

- NIS increased by an average of 12.07 points per year during the tafamidis treatment period
- While NIS increased by an average of 14.36 points per year during the 12 months prior to tafamidis discontinuation, NIS increased at a slower rate of an average of 2.36 points per year during the 12 months following patisiran initiation (**Figure 6**)

Figure 6. Change in NIS over SoC Visits (n=24)



NIS total is graded on a scale of 0–244, with a higher score indicating greater impairment; a 2-point change is considered the least degree of change a physician could recognize. Tafamidis discontinuation visit did not overlap with the eve of patisiran initiation for 4 of 20 patients. Each measurement was allowed to be entered within a ± 90-day window around the patisiran initiation visit, thus the patisiran central tendency extends before Day 0. For some patients, the NIS measurement date closest to the patisiran initiation date was before the patisiran initiation date. **Abbreviations:** NIS, Neuropathy Impairment Score; SoC, standard of care.

Results

Assessment of Walking Difficulties

- Over the tafamidis treatment period, approximately one-third of evaluable patients were considered by the clinician to have a stable walking status since the previous evaluation (**Table 3**)
- Over the 12 months following patisiran initiation, the majority of evaluable patients were reported to have a stable walking status since the previous evaluation (**Table 3**)

Table 3. Walking Difficulties During Tafamidis and Patisiran Treatment

Changes in the Level of Walking Difficulties since the Last Assessment	Initiation of Tafamidis	12 months Prior to Discontinuation of Tafamidis	6 months Prior to Discontinuation of Tafamidis	Discontinuation of Tafamidis	Initiation of Patisiran	6 months After Initiation of Patisiran	12 months After Initiation of Patisiran
Number of patients assessed, n	17	16	19	24	24	18	18
Stable since last evaluation, %	29.4	31.3	21.1	37.5	33.3	83.3	66.7
Stable over the 12 months period, %	—	—	—	0.0	–	—	22.2

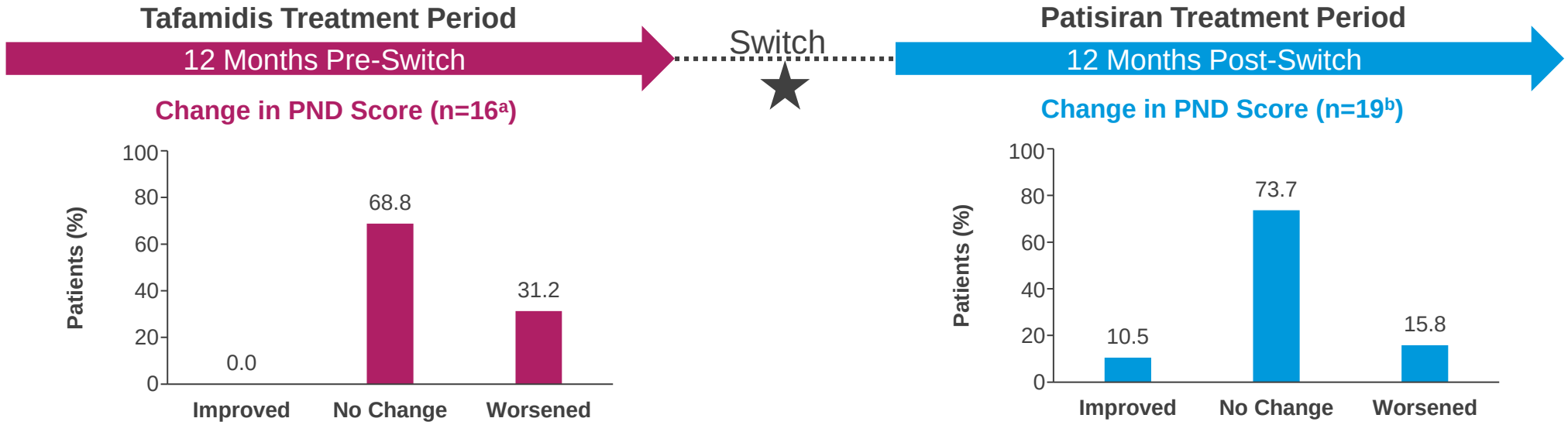
Walking difficulty status, including the investigators' qualitative assessments of the walking distance achieved, presence of a balance disorder, and frequency of falls, was determined as: stable since last evaluation; new decrease of walking distance; worsening of the decrease of walking distance; new falls; worsening of falls; new balance disorder; worsening of balance disorder (>1 category may apply)

Results

PND Score Change Over 12-Month Treatment Periods

- In approximately the last year of tafamidis treatment (mean 11.17 months) among 16 evaluable patients, **68.8%** had no change in PND score (**Figure 7**)
- In approximately the first year of patisiran treatment (mean 11.72 months) among 19 evaluable patients, **84.2%** had no change or improved in PND score (**Figure 7**)

Figure 7. Change in PND Score Over 12-Month Treatment Periods



Worsened (n=5): PND I → II (n=1), I → IIIA (n=1), IIIA → IIIB (n=3)

Worsened (n=3): PND II → IIIA (n=3)
Improved (n=2): PND IIIA → II (n=1), IIIB → IIIA (n=1)

[a]24 (100.0%) patients had a tafamidis discontinuation standard of care visit, 16 patients (66.7%) had a visit 12 months prior to tafamidis discontinuation visit; mean length of the tafamidis assessment period was 11.17 months.
[b]19 (79.2%) patients had a 12-month standard of care visit; mean length of the patisiran assessment period was 11.72 months

Abbreviations: PND, Polyneuropathy Disability.

Results

Safety Summary

- During the first 12 months of treatment, no patients discontinued patisiran to switch to alternative therapies (including tafamidis) for the polyneuropathy of hATTR amyloidosis (**Table 4**)

Table 4. Safety Events that Lead to Potential Unplanned Hospitalization, Extension of an Existing Hospitalization, or Fatality[a]

	During Tafamidis Treatment Period (n=24)	During Patisiran Treatment Period (n=24)
Duration of treatment use (months), mean (SD)	30.05 (17.53)	11.72 (1.35)
Patients with safety event, n (%)	2 (8.33)[b]	3 (12.50)[c]
Result of safety event		
Unplanned hospitalization, n (%)	2 (100.00)	3 (100.00)
Recovery status, n (%)	2 (100.00)	2 (66.67)
Recovered/resolved without sequelae	2 (100.00)	0 (0.00)
Ongoing as of the date of data extraction	0 (0.00)	2 (66.67)
Fatality, n (%)[d]	—	1 (33.33)
Extension of existing hospitalization, n (%)	0 (0.00)	0 (0.00)

[a]Per protocol, there was no attribution of relatedness to treatment of any safety event; [b]Bone pelvic fracture: 1 (4.17%); syncope: 1 (4.17%); [c]Heart failure: 1 (4.17%); left foot tarsal dislocation: 1 (4.17%); vitreous hemorrhage due to severe amyloidosis of the retinous vessels: 1 (4.17%); [d]Fatality is only relevant to the patisiran treatment period

Abbreviations: hATTR, hereditary transthyretin mediated; SD, standard deviation.

Conclusions

- This study summarizes the real-world treatment experience in a single-center cohort of patients who received treatment with tafamidis and then switched to patisiran for the treatment of hATTR amyloidosis with polyneuropathy
- Over the course of tafamidis treatment, patients worsened across multiple measures of polyneuropathy, including walking ability and Neuropathy Impairment Score (NIS), resulting in a switch to patisiran treatment
- On average, the patient cohort experienced stabilization of neurologic impairment on these same measures of polyneuropathy after 12 months of patisiran treatment
- Treatment with patisiran did not return patients to their baseline neurologic function observed prior to tafamidis initiation, emphasizing the importance of monitoring disease progression and considering timely switch to patisiran in patients who experience worsening neuropathy with tafamidis
- While the stabilization in measures of polyneuropathy observed with patisiran treatment is consistent with existing data,[1,2] longer-term follow-up will provide further insights into the long-term benefits of patisiran in patients with hATTR amyloidosis with polyneuropathy

Abbreviations: hATTR, hereditary transthyretin mediated; NIS, Neuropathy Impairment Score.

References: 1. Adams et al. *N Engl J Med* 2018;379:11–21; 21; 2. Adams et al. *Lancet Neurol* 2021;20:49-59

Disclosures

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Abbreviations: GPP3, Good Publication Practice version 3.