Real-World Treatment Patterns in Participants with Transthyretin Amyloidosis with Polyneuropathy Enrolled in the ConTTRibute Registry

Isabel Conceição[1], Thomas Skripuletz[2,3], Steen Hvitfeldt Poulsen[4], Colleen Moffit[5], Shaun Bender[5], Teresa L Kauf[5], Ines Losada Lopez[6,7]

[1]ULS Santa Maria, CAML, Faculdade de Medicina Universidade de Lisboa, Lisbon, Portugal; [2]Department of Neurology, Hannover Medical School, Hannover, Germany; [3]Amyloidosis Center Lower Saxony, Hannover Medical School, Hannover, Germany; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Internal Medicine Department, Hospital Son Llatzer, Palma, Spain; [7]Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain

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Conclusions

- **These data provide much-needed real-world evidence of treatment patterns and discontinuation in patients with ATTRv-PN**
- **Observed treatment persistence was higher with RNAi therapeutics than with other therapy classes**
- **Time to discontinuation of initial ATTR treatment was shorter for patients on TTR stabilizers**
- **Of those who discontinued their initial therapy, the most common reasons provided by the site were disease progression for TTR stabilizers, treatment class switching and adverse event for RNAi therapeutics, and treatment class switching and convenience/preference for ASOs**

Introduction

- ATTR is a progressive and fatal disease caused by toxic misfolded transthyretin accumulating as amyloid deposits in multiple tissues and organs, including the peripheral nerves and heart[1–3]
- ATTRv amyloidosis is a hereditary, multisystem disease that commonly manifests as polyneuropathy, but may also include cardiac manifestations[4]
- Treatments in three therapeutic classes (RNAi, ASOs, TTR stabilizers) are approved for the treatment of ATTRv-PN[4,5]
- Currently, there is little direct, comparative, real-world evidence of use and treatment patterns across these agents

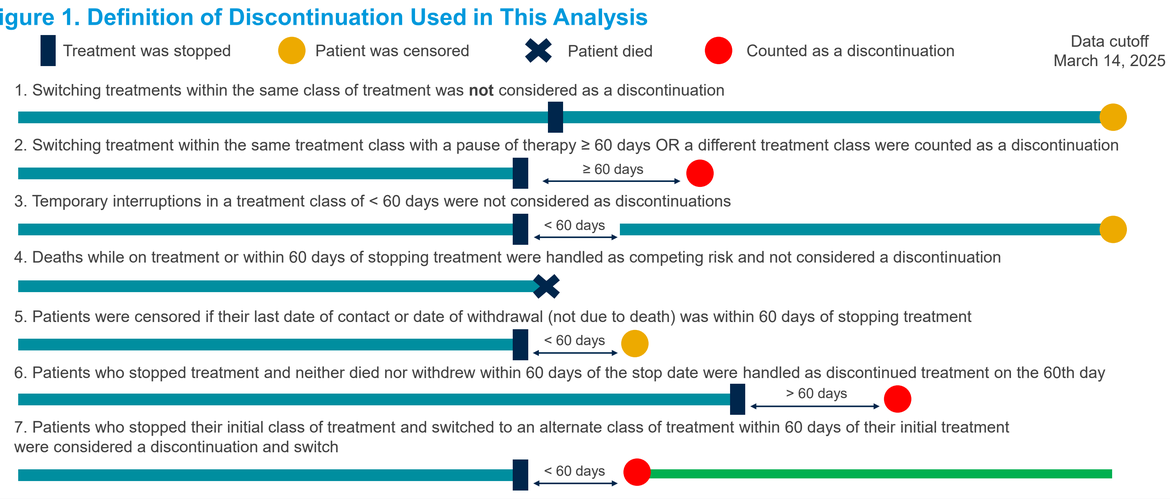
Methods

- ConTTRibute is a global, multicenter, long-term observational study (NCT04561518) designed to document the clinical outcomes of patients with ATTR amyloidosis and asymptomatic carriers of TTR variants
- No visits or examinations, laboratory tests, or procedures are mandated as part of the study
  - Data are collected after each patient visit as part of routine clinical care
- This analysis used retrospective data collected at enrollment and prospective data after enrollment
  - Information on treatment discontinuation was generated by study sites via completion of a discontinuation form

Objective: Evaluate the treatment patterns and use of approved therapies for ATTRv-PN in real- world clinical practice

Patients included in the analysis	Endpoints/outcomes assessed
≥18 years of age not enrolled in a clinical trial	Discontinuations in class of initial ATTR treatment, relative to a patient's first ATTR treatment (**Figure 1**)
Diagnosed with ATTRv-PN at enrollment	Time to discontinuation
Treated with at least one of the following at any point in time before or after enrollment: • RNAi (patisiran or vutrisiran) • TTR stabilizer (tafamidis) • ASO (inotersen or eplontersen)	Reasons for discontinuation
All ATTR treatments were initiated after regulatory approval	Treatment switching (treatment given after stopping initial therapy for patients who discontinued)
At the time of this data cut, only patisiran, vutrisiran, tafamidis, inotersen, and eplontersen were prescribed as ATTR treatments	

Figure 1. Definition of Discontinuation Used in This Analysis



Results

- As of data cut-off (March 14, 2025), 202 participants from 11 countries who were enrolled in the ConTTRibute registry met the criteria for this analysis **(Table 1)**
- Of the 202 eligible participants, 103 (51.0%) started on an RNAi therapeutic, 5 (2.5%) on ASO, and 94 (46.5%) on TTR stabilizer

Table 1. Demographic and Disease Characteristics

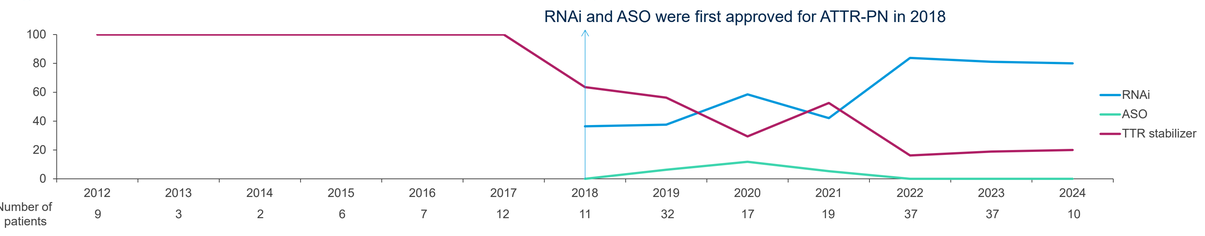
	Initial ATTR treatment		
	RNAi (patisiran/ vutrisiran) (N=103)[1]	ASO (inotersen/ eplontersen) (N=5)	TTR stabilizer (tafamidis) (N=94)
Sex, male, n (%)	66 (64.1)	4 (80.0)	44 (46.8)
Race, n (%)			
White	63 (61.2)	5 (100.0)	80 (85.1)
Asian	24 (23.3)	0	0
Other/not reported/unknown	8 (7.8)	0	14 (14.9)
Black	8 (7.8)	0	0
Age at diagnosis, years, mean (SD)	60.5 (11.6)	65.4 (7.1)	46.8 (15.2)
Time from initial treatment to enrollment, years, mean (SD)*	n=85 1.3 (1.3)	n=5 2.6 (0.9)	n=87 4.9 (3.2)
Time from enrollment to treatment start, years, mean (SD)*	n=18 0.4 (0.5)	n=0 —	n=7 0.3 (0.2)
Genotype			
V30M/V50M, n (%)	36 (35.0)	2 (40.0)	80 (85.1)

	Initial ATTR treatment		
	RNAi (patisiran/ vutrisiran) (N=103)	ASO (inotersen/ eplontersen) (N=5)	TTR stabilizer (tafamidis) (N=94)
Country, n (%)			
Brazil	2 (1.9)	0	8 (8.5)
Denmark	0	0	1 (1.1)
France	5 (4.9)	0	10 (10.6)
Germany	2 (1.9)	0	0
Israel	1 (1.0)	0	4 (4.3)
Italy	14 (13.6)	2 (40.0)	2 (2.1)
Netherlands	4 (3.9)	0	2 (2.1)
Portugal	7 (6.8)	0	44 (46.8)
Spain	2 (1.9)	1 (20.0)	23 (24.5)
Taiwan	24 (23.3)	0	0
United States	42 (40.8)	2 (40.0)	0

*For patients who started treatment prior to enrollment, the time from treatment start to enrollment is reported. For patients who started treatment after enrollment, the time from enrollment to treatment start is reported.

- Demographic and disease characteristics were unbalanced across groups, likely due to the low number of patients in the ASO group and availability of treatments in different countries **(Table 1)**
- The majority of patients receiving a TTR stabilizer as their initial treatment were in Portugal and Spain, with none in the US; more patients had RNAi as initial treatment in the US than other countries; and ASO was initial treatment for a small number of patients in Italy, Spain, and the US

Figure 2. Initial TTR Treatment for Patients in the Analysis



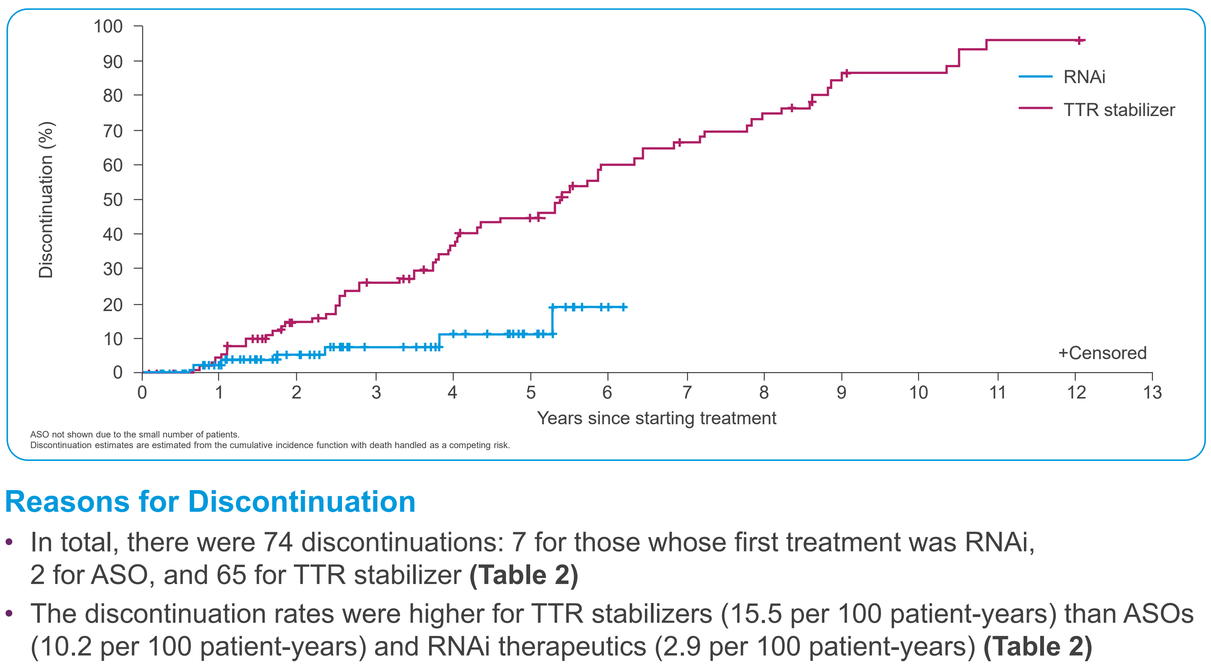
*The total number patients in 2024 decreased due to enrollment being on hold and therefore there were no new patients.

- Prior to the approval of patisiran (2018), 100% of patients received a TTR stabilizer as initial treatment. After 2018, the proportion of patients initially prescribed RNAi increased over time **(Figure 2)**

Observed Treatment Patterns

- Time to discontinuation of initial ATTR treatment was shortest for patients on TTR stabilizers than with RNAi treatments, with approximately three times the proportion of patients discontinuing after six years **(Figure 3)**

Figure 3. Treatment Persistence Was Higher in Patients Whose First Treatment Was RNAi



ASO not shown due to the small number of patients.
Discontinuation estimates are estimated from the cumulative incidence function with death handled as a competing risk.

Reasons for Discontinuation

- In total, there were 74 discontinuations: 7 for those whose first treatment was RNAi, 2 for ASO, and 65 for TTR stabilizer **(Table 2)**
- The discontinuation rates were higher for TTR stabilizers (15.5 per 100 patient-years) than ASOs (10.2 per 100 patient-years) and RNAi therapeutics (2.9 per 100 patient-years) **(Table 2)**
- Of those who discontinued initial therapy, the most common reason given for discontinuation was:
  - TTR stabilizers: Disease progression (60, 92.3%)
  - RNAi therapeutics: Treatment class switching (2, 28.6%) and adverse event (2, 28.6%)
  - ASOs: Treatment class switching (1, 50.0%) and convenience/preference (1, 50.0%)

Table 2. Summary of Site-Provided Reasons for Discontinuation of Initial Treatment

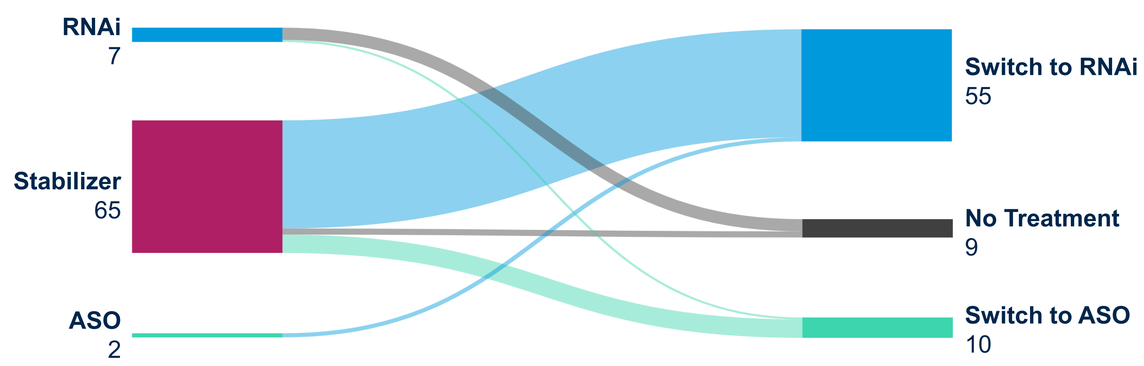
	First treatment		
	RNAi (patisiran/vutrisiran) (N=103)	ASO (inotersen/eplontersen) (N=5)	TTR stabilizer (tafamidis) (N=94)
Number of discontinuations	7	2	65
Patient-years of follow-up	241.0	19.6	418.2
Discontinuations per 100 patient-year (95% CI)	2.90 (1.3, 6.1)	10.20 (2.5, 41.1)	15.5 (12.2, 19.9)
Discontinuation reasons, n (%)			
Due to disease progression	1 (14.3)	0	60 (92.3)
Neuropathy	0	0	52 (80.0)
Neuropathy and cardiac disease	0	0	4 (6.2)
Not listed	1 (14.3)	0	4 (6.2)
Due to switching treatment class	2 (28.6)	1 (50.0)	3 (4.6)
RNAi	1 (14.3)*	1 (50.0)	2 (3.1)
ASO	1 (14.3)	0	0
Not given	0	0	1 (1.5)
Due to adverse event	2 (28.6)**	0	0
Convenience/preference not due to effectiveness of safety	1 (14.3)	1 (50.0)	1 (1.5)
Patient preference	1 (14.3)	0	0
Unknown	0	0	1 (1.5)

Percentages are out of the number of discontinuations within a treatment class.
The discontinuation reasons are listed as reported by the site. Unknown was included as free text in the survey.
Discontinuation rate and 95% CI are from a Poisson model.
*Considered a discontinuation because switch occurred after the 60-day window.
**One patient discontinued patisiran due to an infusion-related reaction and the other discontinued patisiran after complete heart block and pacemaker placement. Both patients resumed RNAi therapy, though outside of the 60-day window.

Treatment Switching

- **Figure 4** shows the treatment given after stopping the initial therapy for those patients who discontinued
  - Of the 65 patients who were initially receiving a TTR stabilizer, 53 (81.5%) switched to an RNAi therapeutic and 9 (13.8%) switched to an ASO
  - Of the 7 patients who were initially receiving an RNAi therapeutic, 1 (14.3%) switched to an ASO
  - 9 patients were not receiving treatment 60 days after stopping initial therapy

Figure 4. Switch Patterns after Discontinuation of Initial Therapy



Discussion

- During the period analyzed, we observed higher persistency among patients who initiated RNAi therapy for treatment of ATTRv-PN than ASOs and TTR stabilizers
- Disease progression was the most common reason provided for discontinuation in patients whose initial treatment was TTR stabilizer
- Adverse event and treatment switching were the most common reasons provided for discontinuation in patients whose initial treatment was RNAi
- Treatment switching and convenience/preference were the most common reasons provided for discontinuation in patients whose initial treatment was ASOs

Limitations

- Small sample size in ASO group
- Analysis does not account for differences in baseline characteristics that may confound the rates of discontinuation
- Registry data collected during routine clinical care is subject to regional variations in practice patterns and local reimbursement or access restrictions
- Analysis uses data prior to enrollment for some patients, which may be less reliable than the data collected prospectively
- While more than one reason may have contributed to the decision to discontinue initial TTR treatment, only one reason was captured in the registry

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Abbreviations: AE, adverse event; ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; ATTRv, hereditary ATTR; ATTRwt, wild-type ATTR; ATTRv-PN, hereditary ATTR with polyneuropathy; PN, polyneuropathy; q6–12 months, every 6–12 months; RNAi, RNA interference; SD, standard deviation; TTR, transthyretin.

References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Patel et al. *Neurol Ther* 2022;11:1595–607; 4. Karam et al. *Muscle Nerve* 2024;69:273–87; 5. European Medicines Agency. 2025. Summary of Product Characteristics (VYNDAQEL). Available from: https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf (last accessed April 10, 2025).

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