Modelling Impact of Improved Diagnosis and Treatment in V122I Related Hereditary Transthyretin Amyloidosis with Polyneuropathy

P 85

Anasheh Halabi[1], Gengshi Chen[2], Timothy Coker[3], Laura Webber[3], Harrison Goldspink[3], Camila Llanes-Kidder[3], Imogen Onno[3], Mia Papas[4], Susan Grandy[5]

[1]Division of Neuromuscular Medicine, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, USA, [2]Global Market Access and Pricing, Health Economics and Payer Evidence, BioPharmaceuticals, AstraZeneca, Cambridge, UK, [3]HealthLumen Ltd., London, UK, [4]US Medical Affairs, BioPharmaceuticals Medical, AstraZeneca, Wilmington, USA, [5]Global Market Access and Pricing, BioPharmaceuticals, AstraZeneca, Wilmington, USA

Objectives

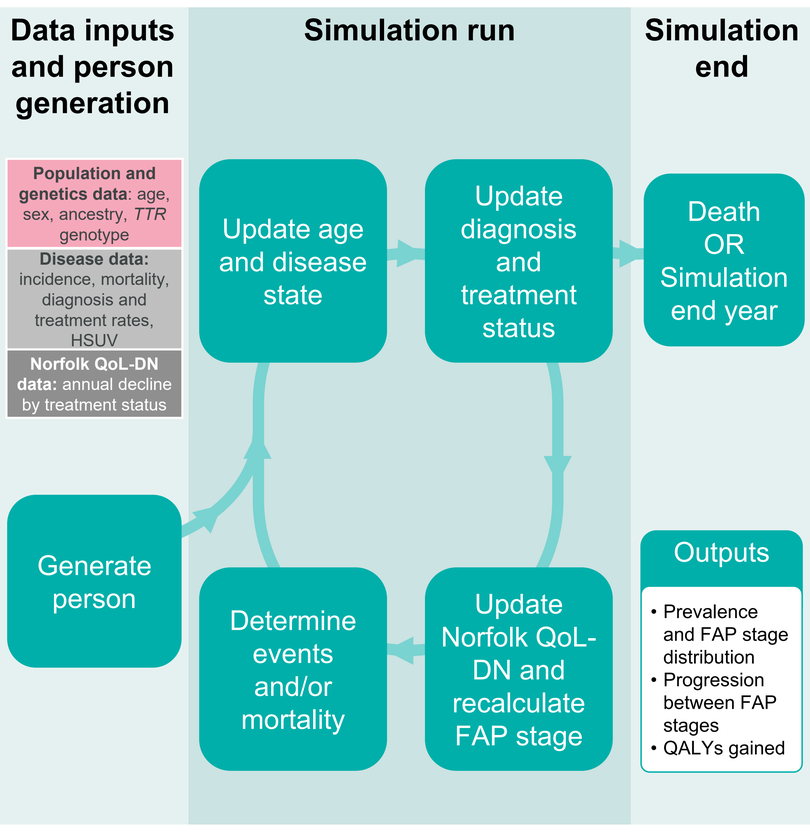
Use a microsimulation model to assess the impact of improved diagnosis and treatment on disease progression in patients with Val122Ile-related hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in the US.

Introduction

- ATTRv-PN is a progressive autosomal dominant disorder that leads to sensorimotor polyneuropathy (PN) and autonomic dysfunction [1].
- If left untreated, ATTRv-PN can cause profound morbidity, particularly in later familial amyloidotic polyneuropathy (FAP) stages of disease [1].
- The Val122Ile (p.Val142Ile) *TTR* variant is the most common ATTRv-associated variant in the United States [2].
- Whilst historically associated with cardiomyopathy (CM), there is increasing evidence that the Val122Ile *TTR* variant is associated with ATTRv-PN as well as a ATTRv-mixed (PN + CM) phenotype [3,4].
- Phenotypic heterogeneity in ATTRv-PN results in delayed diagnosis, treatment, and increased severity [5].
- Improving time-to-diagnosis may delay disease progression, improve quality of life and reduce mortality in patients with Val122Ile-related ATTRv-PN.

Methods

- The microsimulation model incorporated US-specific (or proxy where unavailable) data to create a representative cohort of patients with Val122Ile-related ATTRv-PN or ATTRv-mixed in the US (Figure 1).
  - Patients with ATTRv-CM were excluded from this analysis.
  - The proportion of patients with ATTRv-PN and ATTRv-mixed were derived from a US cohort study [6].
- Individuals were followed in annual cycles from 2025 to 2034, during which they could develop the disease, experience disease progression, receive diagnosis and/or treatment, or die.
  - In the absence of prevalence data, the model was calibrated to an assumed baseline prevalence of 1,000 patients in 2025.
- FAP stage progression was characterised by annual Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) decline derived from trial data [7], with Norfolk QoL-DN scores being mapped to FAP stage based on a mapping algorithm [8]:
  - Norfolk QoL-DN scores of ≥ 2.6 and < 54 corresponded to FAP stage 1, Norfolk QoL-DN of ≥ 54 and < 91 corresponded to FAP stage 2 and scores ≥ 91 corresponded to FAP stage 3.



FAP, Familial Amyloidotic Polyneuropathy; HSUV, Health state utility value; Norfolk QoL-DN, Norfolk Quality of Life Diabetic Neuropathy; QALYs, Quality-adjusted life years

Figure 1. Schematic of the microsimulation model

Methods continued

- Patients with diagnosed ATTRv-PN could be treated with a silencer, whilst patients diagnosed with ATTRv-mixed could be treated with either a silencer or a stabiliser.
  - The split of silencer-to-stabilizer treatment was 60.6% and 39.4% in 2025, and 67% and 33% in 2034 [9].
- Current practice and intervention scenarios were run and compared (Figure 2).

Current Practice Scenario	Intervention Scenario
'No change' scenario reflecting current standard of care	Improved diagnosis and treatment for patients with PN symptoms
Diagnosis • Current time-to-diagnosis (average 2.9 years ATTRv-PN; 2 years ATTRv-mixed) [10] • An assumed 41.5% prevalent diagnosis rate Treatment • 20% of diagnosed patients with ATTRv-PN were treated in 2025; 25% of diagnosed ATTRv-mixed [11] • Assumed linear increase to 30% (ATTRv-PN) and 35% (ATTRv-mixed) by 2034	Diagnosis • Assumed halved time to diagnosis from 2025 • 100% of incident patients with ATTRv-PN and patients with ATTRv-mixed were diagnosed from 2025 Treatment • 100% of incident patients with ATTRv-PN and patients with ATTRv-mixed were treated from 2025

Figure 2. Specifications for the current practice and intervention scenarios

Results

Diagnosis and treatment over time

- In the current practice scenario, 40% of patients with Val122Ile-related ATTRv are expected to be diagnosed in 2034, totalling 532 patients (76 patients with ATTRv-PN, 456 patients with ATTRv-mixed). Of those diagnosed, 182 patients (34%) are treated (22 patients with ATTRv-PN, 160 patients with ATTRv-mixed), with 129 patients on silencers, and 53 on stabilisers.
- In the intervention scenario, 70.5% of patients with Val122Ile-related ATTRv are expected to be diagnosed by 2034 (an additional 478 patients) compared with the current practice scenario. Of those diagnosed, 895 (89%) are treated, with 638 patients on silencers, and 257 on stabilisers (Figure 3).

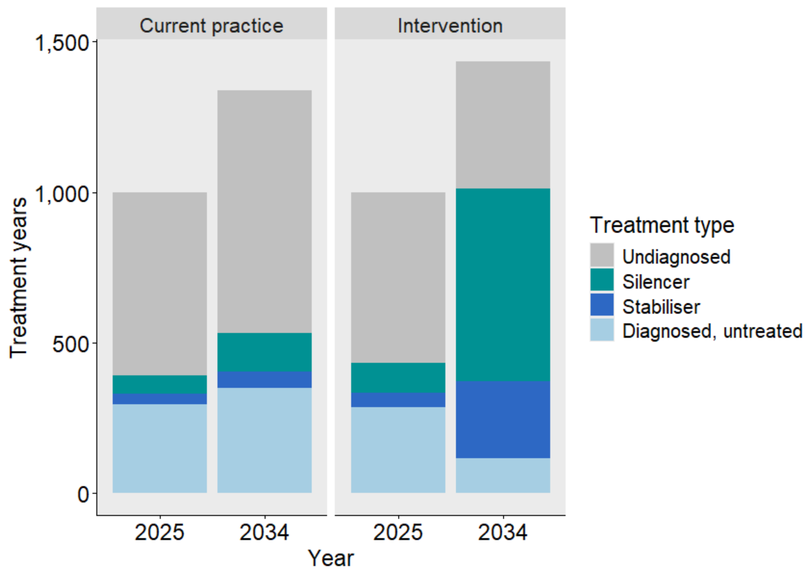


Figure 3. Diagnosis and treatment rates in the two scenarios

FAP stage distribution

- In the current practice scenario, 706 patients with Val122Ile-related ATTRv are estimated to be in FAP stage 1, 92 in stage 2, and 203 in stage 3 in 2025. By 2034, an additional 243 patients are projected to be in FAP stage 1, 31 in FAP stage 2, and 63 in FAP stage 3.

Results continued

- In the intervention scenario, 173 additional patients in FAP stage 1 are projected in 2034 compared to current practice. There are 34 fewer patients in FAP stage 2, and 41 fewer patients in FAP stage 3 projected compared with current practice, representing a 27.9% and 15.3% decrease, respectively (Figure 4).

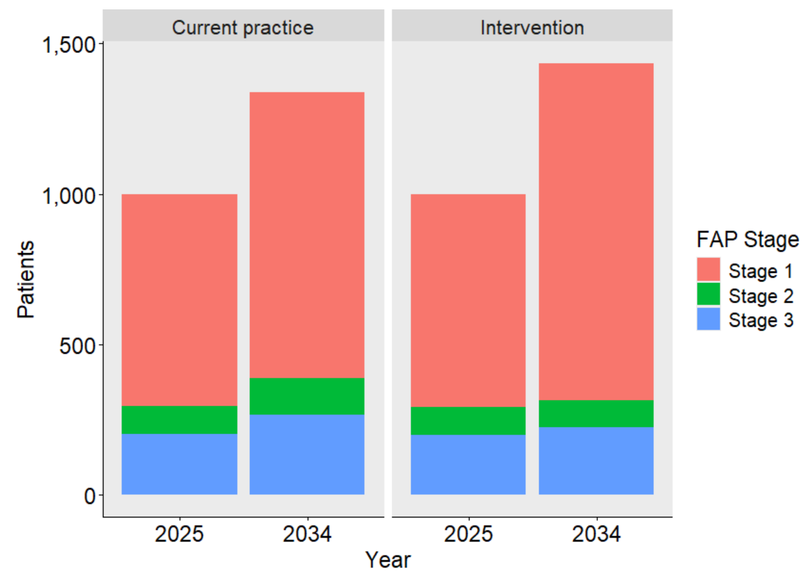


Figure 4. FAP stage distribution of patients with ATTRv-PN in the two scenarios.

Cumulative disease progression avoided in the intervention scenario

- Over the 10-year period, a 24.5% reduction in progression to more severe FAP stages is projected under the intervention scenario, with 158 fewer patients (34 fewer patients with ATTRv-PN, 124 fewer patients with ATTRv-mixed) progressing from FAP stage 1 to FAP stage 2, and 85 fewer patients (19 fewer patients with ATTRv-PN, 66 fewer patients with ATTRv-mixed) progressing from FAP stage 2 to FAP stage 3 (Figure 5).

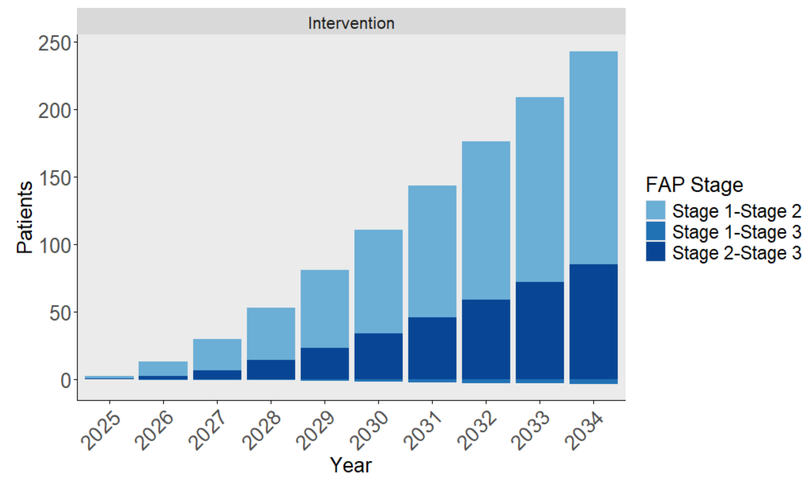


Figure 5. Cumulative disease progression avoided in the intervention scenario relative to current practice

Quality-adjusted life years (QALYs) gained in the intervention scenario

- Over the 10-year period, a total of 436 QALYs are gained in the intervention scenario compared with the current practice scenario, driven by the reduction in FAP stage 2 and 3 patients by 2034.

Conclusion

- Earlier diagnosis and treatment with silencers are projected to reduce progression to FAP stage 2 and 3 in patients with Val122Ile-related ATTRv by 24.5% and reduce prevalence of severe disease by 19.3% by 2034.
- This reduction in disease severity is associated with an estimated 436 QALYs gained, reflecting patients' longer lives and better health-related quality of life.
- These findings underscore the importance of timely diagnosis and treatment of patients with Val122Ile-related ATTRv-PN and ATTRv-mixed.

References: [1] Adams, D., et al., *Expert Consensus Recommendations to Improve Diagnosis of ATTR Amyloidosis with Polyneuropathy.* Journal of Neurology, 2021. **268**(6): p. 2109-2122. [2] Bhatt K, Delgado DH, Khella S, et al. Hereditary Transthyretin Amyloidosis in Patients Referred to a Genetic Testing Program. J Am Heart Assoc. 2024;13(23):e033770. doi:10.1161/JAHA.123.033770 [3] Parker, M.M., et al., Association of the transthyretin variant V122I with polyneuropathy among individuals of African ancestry. Scientific Reports, 2021. 11(1): p. 11645. [4] Zampino, S., et al., Phenotypes Associated With the Val122Ile, Leu58His, and Late-Onset Val30Met Variants in Patients With Hereditary Transthyretin Amyloidosis. Neurology, 2023. 100(19): p. e2036-e2044. [5] Wang, T.-W., et al., *Updates on Hereditary Transthyretin Amyloidosis Polyneuropathy.* Journal of the Formosan Medical Association, 2026. [6] Qarni, T.N., et al., Treatment characteristics of patients with hereditary transthyretin amyloidosis: a cohort study. Orphanet Journal of Rare Diseases, 2024. 19(1): p. 191. [7] Coelho, T., et al., *Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy.* Jama, 2023. **330**(15): p. 1448-1458. [8] Faria, R., et al., *Tafamidis for Transthyretin Familial Polyneuropathy (TTR-FAP) Evidence Review Group assessment of manufacturer submission.* 2012. p. 1-187. [9] Grogan, M., et al., MaesTTRo: Initial Findings From a Pioneering Prospective Multi-Country Real-World Study of Patients With Transthyretin Amyloidosis, in European Society of Cardiology (ESC) Congress 2025. 2025: Madrid, Spain. [10] Anderson, L., et al., *Early Clinical Manifestations and Time-To-Diagnosis in Patients with ATTR Amyloidosis With Mixed Phenotype - Results From the OverTTuRe Study*, in *European Society of Cardiology Heart Failure (ESC-HF) Congress 2025.* 2025: Belgrade, Serbia. [11] Bazell, C., et al., *Descriptive characteristics of patients diagnosed with transthyretin amyloidosis (ATTR) in the Medicare fee-for-service and commercial populations*, in *International Symposium of Amyloidosis 2024*. 2024: Rochester, MN.

Presented at PNS, 13th – 16th June 2026 *Supported by* AstraZeneca

Presenting author's contact information - gengshi.chen@astrazeneca.com