



# **Patisiran & Inotersen for Treatment of Hereditary Transthyretin Amyloidosis: Effectiveness and Value**

**Modeling Analysis Plan**

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# 1. Approach

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The primary aim of this analysis will be to estimate the cost-effectiveness of patisiran and inotersen for the treatment of hereditary transthyretin amyloidosis (hATTR). The model will compare patisiran and inotersen with best supportive care (i.e., trial placebo arms). The base case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime horizon. A modified societal perspective including productivity losses and other indirect costs (as available) will be considered in a dual base case, as this product falls under ICER’s ultra-rare disease definition. Figure 1 depicts the analytic framework for this assessment. The model will be developed in Microsoft Excel.

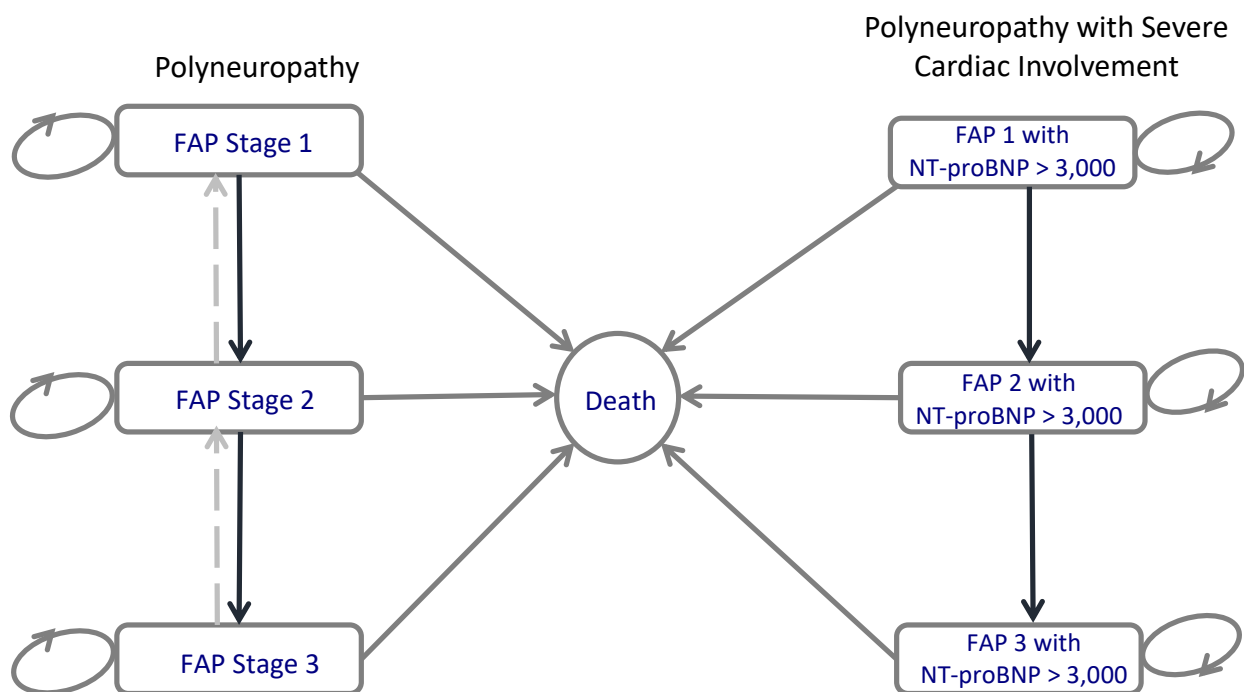
## 2. Methods

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### 2.1 Overview and Model Structure

The model uses one-month cycle lengths over a lifetime horizon.

**Figure 1. Model Framework**



## 2.2 Target Populations

The target population for this economic evaluation is adults with hereditary ATTR (hATTR) amyloidosis, with an indication for treatment with patisiran or inotersen. Since differences in the primary outcome measures and trial populations (e.g., disease severity) preclude direct comparison of the APOLLO and NEURO-TTR trials, there will be two separate cohorts for the base case models—one for each drug, with characteristics based on each trial’s baseline population (Table 1).

**Table 1. Base-Case Model Cohort Characteristics**

	Value	Primary Source
<b>For the patisiran model:</b>		
Mean age	62	Adams et al. <sup>1</sup>
Female	26%	Adams et al. <sup>1</sup>
FAP Stage 1	46.2%	Adams et al. <sup>1</sup>
FAP Stage 2	53.8%	Adams et al. <sup>1</sup>
Severe Cardiac Involvement (NT-proBNP > 3,000)	12.9%	Slama et al. <sup>2</sup>
<b>For the inotersen model:</b>		
Mean age	59	Benson et al. <sup>3</sup>
Female	31%	Benson et al. <sup>3</sup>
FAP Stage 1	67%	Benson et al. <sup>3</sup>
FAP Stage 2	33%	Benson et al. <sup>3</sup>
Severe Cardiac Involvement (NT-proBNP > 3,000)	14.2%	Proportional assumption based on relative frequency of general cardiac sub-populations in main trials for inotersen (75/112 or 67.0%) and patisiran (90/148 or 60.8%), yielding $12.9\% \times 1.1 = 14.2\%$

## 2.3 Interventions

The full list of interventions is as follows:

- Patisiran (0.3 mg/kg infusion every three weeks)
- Inotersen (once-weekly 300 mg subcutaneous injections)

If data deemed essential to the model are not received from the pharmaceutical manufacturer, it is possible an intervention’s cost-effectiveness will not be modeled.

### Comparators

The comparator in clinical trials was placebo, reflecting best supportive care. Both diflunisal and tafadimis were excluded from consideration as neither has received FDA approval for the treatment of hATTR. Given the heterogeneity in the trial populations for patisiran and inotersen, separate models (comparing the drug to best supportive care) are proposed for each intervention.

## 2.4 Key Model Choices and Assumptions

Key assumptions to be used in the economic model are listed in Table 2.

**Table 2. Key Model Assumptions**

Assumption	Rationale
The disease can be modeled similarly regardless of the genetic variant.	There are not sufficient data to make separate models for each genetic variant.
Disease heterogeneity can be separated into FAP stage progression and severe cardiac involvement (defined as NT-proBNP > 3,000).	Clinically, patients have the potential to experience both polyneuropathy and cardiac symptoms. Separate disease states are needed to capture the differing costs, quality of life, and mortality impacts when NT-proBNP increases above 3,000.
Mortality by FAP stage can be approximated by data outside of the trials (e.g., Adams, 2013 <sup>4</sup> and Swiecicki et al. 2015) <sup>5</sup> .	There are no trial data on mortality by FAP stage. This was approximated based on mortality data for patients with any or advanced neuropathy.
AEs are not modeled separately.	Any events with an apparent excess risk (e.g., thrombocytopenia) would be unlikely to materially affect model findings.
Patients do not undergo liver transplantation.	Clinical expert opinion indicated that this procedure is no longer a common treatment for these patients.
Severe cardiac involvement (NT-proBNP > 3,000) leads to a 10% decrement in the quality of life utility for each FAP stage.	This estimate is based on the 10% decrement for heart failure reported in Sullivan and Ghushchyan, 2006. <sup>6</sup>
Patients stay on treatment until death.	This assumption is varied in scenario analyses.

## 2.5 Input Parameters

### Clinical Inputs

The clinical inputs are from diverse sources (e.g., published papers vs. conference abstracts). As a result, it is necessary to calibrate the resulting transition probabilities so that all probabilities sum to one. The transition to the death state can be related to natural causes, polyneuropathy or severe cardiac involvement (NT-proBNP > 3000). The natural cause death rate comes from the CDC tables. The death rate from polyneuropathy depends on FAP stage. FAP Stage 1, Stage 2 and Stage 3 are approximated by the “without neuropathy” curve, the “with neuropathy” curve, and the “with weight loss” curve, respectively, from the article by Swiecicki et al. The death rate related to severe cardiac involvement (NT-proBNP > 3000) is taken from the poster by Slama et al. The rates reported in the poster and publication are then converted into probabilities that match the model’s cycle length.

### Transition Probabilities/Response to Treatment

The transition probabilities between FAP stages are derived from the poster by Gonzalez-Duarte et al. The categories reported are 1) Improved, 2) No change, 3) Worsened, and 4) Missing. The reported percentages in these four categories by treatment type can be combined with the initial distribution of the FAP stages reported in the poster. The data in the Missing category were redistributed by first netting out the trial participants who died and then assuming the remaining amount could be reclassified as: 2) No change and 3) Worsened, in a 50/50 split. The difference in these percentages provides the evidence of a benefit from treatment. Age-specific mortality rates come from the U.S. Social Security Administration life tables.

### Health State Utilities

Health state utility weights assigned to each FAP stage were adjusted by a quality of life decrement to serve as a “toll” for severe cardiac involvement (NT-proBNP > 3,000). The utilities for FAP stages 1 and 2 are from the trial data reported by Denoncourt et al.<sup>7</sup> The missing FAP stage 3 utility value is taken from the “by stage” estimation of Disease Stage 3 in the tafamadis report produced by the York Economic Review Group (ERG).<sup>8</sup> The York ERG crafted crosswalk equations for the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire (abbreviated TQoL in their report) and the EQ-5D utility scores needed for economic evaluations. In the York ERG’s analysis, the EQ-5D data come from an analysis using the THAOS (Transthyretin Amyloidosis Outcomes Survey) data collected in a longitudinal, observational survey studying the natural history of patients with hATTR. The utility decrement for severe cardiac involvement (NT-proBNP > 3,000) is assumed to be a 10% disutility, reflecting the 10% decrement estimated for heart failure reported by Sullivan and Ghushchyan, 2006.<sup>6</sup>

The utility parameters were varied in both scenario and sensitivity analyses to explore the impact of uncertainty. Additionally, we explored the impact of using different sets of utility values (e.g., those reported by the York Economic Review Group).<sup>8</sup>

**Table 3. Utility Values for Health States**

Health state	Utility value If NT-proBNP < 3000	Utility value If NT-proBNP > 3000
FAP Stage 1	0.710	0.639
FAP Stage 2	0.570	0.513
FAP Stage 3	0.170	0.153

Patients in both the NEURO-TTR trial (taking inotersen) and the APOLLO trial (taking patisiran) reported improvements in Norfolk QOL-DN compared to placebo. Norfolk QOL-DN scores may be

mapped to EQ-5D quality of life utilities, allowing differences in QoL score to be converted into a utility value. We will explore using this method to include an additional utility improvement within FAP stage.

## Adverse Events

To ensure comparability with most previously published cost-effectiveness analyses, this analysis will not include adverse events in the base case analysis.

## Cost Inputs

### *Drug Acquisition Costs*

In the absence of actual drug prices for both treatments, the drugs will be assumed to have a placeholder cost of \$300,000 per year, based on investment analyst estimates.<sup>9</sup> For patisiran infused in-clinic, additional costs of administration and facility mark-up will be included.

For inotersen, the \$300,000 drug cost is not accompanied by any induction or monitoring costs; however, for the first year inotersen’s treatment will be assumed to include a \$74.16 fee, representing a one-time training cost for self-injection (CPT code 99213: national non-facility price = \$74.16), with subsequent years of inotersen assumed to be \$300,000.

**Table 4. Drug Cost Inputs**

Intervention	Dosing and Route of Administration	Drug Cost per Dose	Annual Drug Cost	Annual Other Drug Costs	Annual Total Drug Cost*
Patisiran (infused 100% in-clinic)	0.3 mg/kg IV	\$17,260.27	\$300,000	\$22,015.17	\$322,015.17
Inotersen	300 mg SC	\$5,754.85 the 1 <sup>st</sup> year and \$5,753.42 afterward	\$300,000	\$74.16 the 1 <sup>st</sup> year and \$0 afterward	\$300,074.16 the 1 <sup>st</sup> year and \$300,000 afterward

\*Note: Assuming a 10%/90% split between at-home and in-clinic infusion, the annual total drug cost is \$319,818.69. Including a 1-time \$74.16 training cost for inotersen increases the year 1 annual total drug cost to \$300,074.16 for inotersen. After the first year, inotersen’s annual cost is assumed to be \$300,000.

### *Administration and Monitoring Costs*

For patisiran infused in-clinic, additional costs will include:

- 6% mark-up to the drug’s annual acquisition cost ( $\$300,000 \times 6\% = \$18,000$ );
- \$228.11 administration cost per infusion (up to 1 hour + additional infusion time: CPT code 96365 + 96366 =  $\$191.08 + \$37.03$ ); and

- \$2.90 for pre-infusion drugs at generic WAC prices per infusion (10 mg dexamethasone at \$2.70, 500 mg oral acetaminophen at \$0.05, 50 mg diphenhydramine at \$0.10, and 50 mg ranitidine at \$0.05).

Patients taking a drug administered subcutaneously will be assumed to incur the cost of one additional clinic visit at which instruction takes place, after which they self-administer the drug.

The drugs included in this study may require that patients have tests prior to and/or during treatment. We will therefore add to the cost of treatment any such tests for each drug.

#### *Health Care Utilization Costs*

The health care utilization costs are computed by taking the quantities from the Schmidt et al. poster<sup>10</sup>, which reports annual service use by patients in the year prior to the APOLLO trial. We will apply 2018 costs for the relevant CPT codes. Since there are no data for FAP stage 3 participants, we will assume the costs for FAP stage 3 as 35% more than for FAP stage 2. The 35% assumption is an average of the percentage increase in FAP stage 3 costs reported in a poster by Inês et al. (37% increase) and the report by the York Economic Review Group (33% increase).<sup>8,11</sup> People with severe cardiac involvement (NT-proBNP > 3000) at baseline will be assumed to have \$85,964 in additional costs per year, equal to two hospital visits (for DRG 291: Heart failure & shock with major complication or comorbidity).<sup>12</sup> Lastly, we will include a one-time cost of \$41,160 when patients transition to death. This estimate is based on the difference between the cost of decedents and the cost of survivors reported in Riley and Lubitz (2010).<sup>13</sup> All costs will be adjusted to 2018 US dollars.

#### *Productivity Costs*

Productivity costs will be included in a dual base case analysis, as per ICER's Value Framework for rare diseases. Estimates for the lost work hours associated with each FAP stage will use data from the posters by Berk et al. and Schmidt et al.<sup>10,14</sup> Given there are no estimates for productivity costs accrued in FAP stage 3, we will assume they are the same as those in FAP stage 2. This assumption was also made by the York ERG in their cost-effectiveness analysis of hATTR treatment.<sup>8</sup> In addition, we will include an estimate of hours of informal caregiving attributable to cardiovascular disease from Dunbar et al. to approximate the additional productivity costs of severe cardiac involvement.<sup>15</sup> We will use a \$24.23 per hour average hourly wage (U.S. Bureau of Labor Statistics) to create an "hourly price" for that time.



## 2.6 Model Outcomes

As the primary outcomes, the model will estimate expected costs, life-years, and quality-adjusted life-years (QALYs). We will also calculate incremental cost per life-year and per QALY.

## 2.7 Analysis

Each model cycle lasts one month. Patient survival, quality-adjusted survival, and costs will be estimated for each model cycle and then summarized over lifetime horizons for each treatment option. Differences in survival, quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

### Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

### Scenario Analyses

We will perform several scenario analyses based on modifying one or more of the base case values for the parameters related to initial FAP stage distribution, QALYs, and costs. Additionally, we will perform a threshold analysis by systematically altering the price of each drug to estimate the maximum prices that would correspond to willingness to pay (WTP) thresholds of \$50,000, \$100,000, \$150,000, \$250,000 and \$500,000 per QALY.

### Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

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