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Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value

Final Background and Scope
April 9, 2018

Hereditary transthyretin amyloidosis (hATTR) is a multi-system illness caused by misfolding deposits of transthyretin (TTR), a protein that is present in all human serum. Genetic mutations can increase the likelihood of TTR misfolding into an insoluble beta-pleated sheet, which deposits in body tissues. A rare, progressive, and fatal autosomal dominant hereditary disorder, hATTR symptoms span a spectrum of clinical presentations. These presentations include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy) and a predominatly cardiac phenotype (formerly known as familial cardiomyopathy). Disease symptoms, age of onset, and rate of progression are highly variable from patient to patient,[1] and many patients have both cardiac and neurologic involvement. In addition, other organ systems may be affected (e.g., gastrointestinal, renal, and ocular effects), particularly as the disease progresses.[1] The illness affects at least 10,000 people worldwide, and roughly 3,000-3,500 people in the US.[2,3] Due to under-diagnosis, the true number of affected individuals is likely greater.

The neurologic symptoms of hATTR are among the most disabling. Deposition of TTR-derived amyloid fibrils produces severe sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and bowel or bladder dysfunction.[4] The cardiac manifestations of hATTR include arrhythmias, an enlarged heart (cardiomegaly), and orthostatic hypertension. If the disease is untreated, median survival is between 3-15 years from the onset of hATTR.[1] The age at onset varies from the second to ninth decade of life.[1] For patients with the early onset genetic mutation known as Val30Met, a mutation common in Portugal, researchers have estimated mean lifetime health care costs of 125,645€ ($154,819) per untreated patient.[5]

While there is no treatment available that reverses damage caused by amyloid deposits, and there is currently no FDA-approved treatment available in the US, there are treatments that may prevent or delay progression.[6] The liver produces almost all of the body's TTR. Therefore, liver transplantation, which removes the abnormal TTR, is one potential treatment. Limitations of this approach include transplant availability, disease progression following transplant (e.g. of hATTR cardiomyopathy), and substantial morbidity and mortality associated with transplant itself. Further, liver transplant benefits only a select group of patients with hATTR, such as those with early-onset of amyloidosis caused by the Val30Met mutation.[7]

Diflunisal, a generic nonsteroidal anti-inflammatory drug (NSAID) which stabilizes transthyretin tetramers, is one off-label treatment available in the United States. In a randomized trial of 130 patients with symptomatic hATTR, diflunisal significantly reduced progression of neurologic impairment at two years and preserved quality of life compared to placebo.[8] However, use of diflunisal is limited by risks of gastrointestinal bleeding and worsening of renal insufficiency.

Tafamidis, a TTR stabilizer administered orally once daily, is the only medicine approved to delay disease progression in hATTR, and is approved in the European Union and several South American and Asian countries.[9-11] However, the US FDA did not approve its use during a filing in 2012, due to limited efficacy data.[12]

In addition, there are two investigational agents currently under FDA review for hATTR: patisiran (Alnylam Pharmaceuticals) and inotersen (Akcea Theraputics). Patisiran is an RNA interference (RNAi) therapeutic.[13,14] An IV infusion, patisiran suppresses the production of both mutant and nonmutant forms of TTR. Inotersen is an antisense oligonucleotide (ASO) that complements exactly the messenger RNA (mRNA) that encodes for TTR. A once weekly subcutaneous injection, inotersen binds the mRNA leading to degradation of TTR by RNAase. In Phase III clinical trials, both agents improved measures of neuropathy impairment, the primary study outcome, and health-related quality of life. Secondary endpoints included modified body mass index (mBMI; the product of serum albumin concentration and BMI) and NT-proBNP, a measure of left ventricular cardiac function, both of which have been found to be predictors of survival in hATTR.[15,16] Other exploratory cardiomyopathy endpoints (e.g., ejection fraction, left ventricular size) were also included in the studies and may be relevant for this evaluation.

As the first agents targeting the production of the protein inducing hATTR, clinical interest in the use of patisiran and inotersen is likely to be high. However, there may be uncertainties related to the translation of surrogate outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications. All stakeholders will therefore benefit from a comprehensive review of the comparative clinical effectiveness, safety, and economic impact of patisiran and inotersen relative to standard care for hATTR.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, patient advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public.

Patients, patient advocates, and researchers have conveyed that hATTR is a severe disabling illness that profoundly impacts all aspects of quality of life. Given that the disease may affect multiple

organ systems and may progress rapidly, a wide variety of manifestations may include (but are not limited to) weight loss, wasting, difficulty walking, and alternating constipation and uncontrollable diarrhea. Patients with hATTR are frustrated by loss of independence. Not only are patients unable to work, but they may also have difficulty leaving the house and ultimately, may become bed-bound and unable to dress, feed, or bathe themselves. Patients describe a devastating impact of the illness on family life, with members of multiple generations of the same family affected. Some individuals care for older family members who are affected while also worrying about children who carry the mutation. Patients voice concern that in the face of such suffering, there are currently no treatments approved in the US specifically for hATTR. Current off-label treatments are of limited efficacy, and patients often have difficulty travelling to a small number of Amyloid Centers of Excellence at academic medical centers in the US to receive treatment.

This final scoping document incorporates feedback gathered during preliminary calls with stakeholders and following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review of inotersen and patisiran for hATTR and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Potential Major Advance for a Serious Ultra-Rare Condition:

We propose to assess patisiran and inotersen under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because we believe the assessment meets the following proposed criteria:

- *The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.*
- *There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.*

As noted above, the estimated diagnosed prevalence in the U.S. is approximately 3,000-3,500, and is not likely to exceed 10,000 even with the potential for under-diagnosis.

Report Aim

This project will evaluate the health and economic outcomes of patisiran and inotersen for hATTR. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

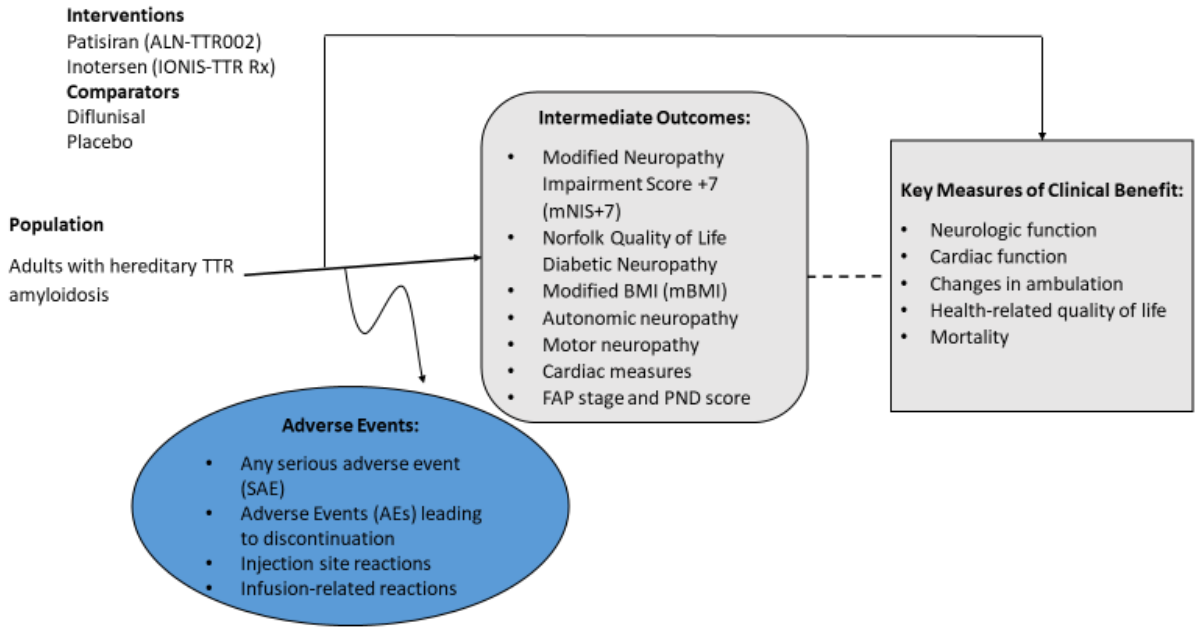
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for hATTR is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Therapies for Hereditary TTR amyloidosis (hATTR)



AE: adverse event, SAE: serious adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g. neuropathy impairment score), and those within the squared-off boxes are key measures of benefit (e.g., quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.

Populations

The population of focus for the review is adults with hereditary ATTR (hATTR) amyloidosis.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Patisiran
- Inotersen

Comparators

The comparator in clinical trials was placebo, reflecting best supportive care. Data permitting, we also intend to compare the investigational agents to each other as well as to diflunisal.

Outcomes

The outcomes of interest are described in Table 1.1 below.

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
Neuropathy (e.g., Modified Neuropathy Improvement Score)	Significant adverse events
Modified BMI (BMI x albumin)	Adverse events leading to discontinuation
NT-proBNP	Injection site reactions
Living independently	Thrombocytopenia (platelet count decrease) causing significant bleeding
Mobility	Infusion-related reactions
Pain	Grades 3 and 4 serious adverse events
Ability to attend to activities of daily living	Death
Health-related Quality of life	
Cardiac function (e.g., ejection fraction, left ventricle mass, NT-proBNP)	
Mortality	

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three months' duration.

Settings

All relevant settings will be considered, including both outpatient and inpatient settings in the United States.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 1.2.

Table 1.2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the cost-effectiveness of the treatments of interest (inotersen and patisiran) relative to conventional support therapy that has available clinical and economic evidence for the treatment of patients with hereditary ATTR (hATTR) amyloidosis. A cohort of patients will transition between health states during predetermined cycles over a lifetime time horizon. The model will include one event, liver transplant, and 5 health states: (i) disease stage 1, where the patient does not require assistance with ambulation or daily function, (ii) disease stage 2, where the patient requires carer assistance and/or a walking aid, (iii) disease stage 3, where the patient is bed-bound, (iv) post-liver transplantation; and (v) death. The model will follow patients from treatment initiation until death, given available evidence. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years)

and if possible for patient subgroups, reflecting heterogeneity by genetic mutation (e.g., Val30Met vs. non-Val30Met).

Under ICER's modifications to the value assessment framework for treatments for ultra-rare diseases, we will consider dual "base cases," which will reflect the health system (i.e., a focus on direct medical care costs only) and modified societal perspectives. A modified societal perspective is included if appropriate data are available, and if it is anticipated that the impact of the treatment on patient and caregiver productivity, education, disability, and nursing home costs are both substantial and large relative to health care costs. If not assessed as a dual base case, a modified societal perspective will be considered in a scenario analysis.

Model inputs will be informed by existing clinical evidence and any published economic evaluations. Key model inputs will include clinical probabilities, overall survival, occurrence of adverse events, quality of life values, and health care costs. Treatment effectiveness will be estimated using estimates of patient response using validated neurologic and/or cardiovascular measures, which may be obtained as point estimates or through meta-analyses of available data. Probabilities, costs, and other inputs may differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical as well as indirect costs. The health outcome of each intervention will be evaluated in terms of life-years and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state. The model will include direct medical costs, including but not limited to costs related to condition-related care and serious adverse events. Relevant pairwise comparisons will be made between treatments (when feasible), and results will be expressed in terms of the incremental cost per QALY gained, cost per life-year gained, and cost per intermediate outcome (e.g., treatment response) achieved.

In a separate analysis, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment price and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by patisiran or inotersen, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hATTR beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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