

# Disease Modifying Therapies for the Treatment of Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM)

## Draft Background and Scope

March 7, 2024

### Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of heart muscle disease that occurs when amyloid fibrils – clumps of misfolded proteins – are deposited into heart tissue and cause it to stiffen.<sup>1</sup> Eventually, the heart cannot fill properly, leading to shortness of breath, heart failure, and death. Prior to the availability of disease-specific therapies, annual ATTR-CM care was estimated to cost more than \$60,000 per patient, mostly related to inpatient hospital care.<sup>2</sup>

There are two types of ATTR-CM that differ in the mechanisms of amyloid protein deposition. In hereditary ATTR-CM, individuals inherit a mutated transthyretin gene that leads to protein misfolding, often causing disease at a younger age.<sup>1</sup> In wild-type ATTR-CM, there is no inherited mutation but transthyretin still misfolds and deposits in the heart, generally occurring in older ages. Hereditary ATTR-CM is more common in people of African descent, often caused by the Val122Ile mutation.<sup>3</sup> This form of the disease also occurs more frequently in women.<sup>4</sup> Hereditary ATTR-CM tends to have a worse prognosis compared to wild-type.<sup>5</sup> Wild-type ATTR-CM accounts for approximately 90% of cases.<sup>6</sup>

The prevalence of transthyretin ATTR-CM is difficult to estimate, given likely underdiagnosis and changes in diagnostic modalities over time. However, it's estimated that more than 120,000 U.S. adults have ATTR-CM, with 5,000 to 7,000 new cases diagnosed each year.<sup>1,7</sup> Historically, many individuals with ATTR-CM received no disease-specific treatment and those with hereditary forms could sometimes receive cardiac transplantation.<sup>8</sup> The first treatment specific to ATTR-CM, tafamidis, a stabilizer of transthyretin, was approved by the FDA in 2019.<sup>9</sup>

Acoramidis, also a transthyretin stabilizer, is under evaluation by the FDA with a PDUFA date of November 29, 2024.<sup>10,11</sup> Another treatment strategy is to use RNA silencing to reduce production of transthyretin.<sup>12</sup> Vutrisiran and eplontersen are RNA silencing agents approved for the treatment of nerve pain and dysfunction from ATTR and are being evaluated for treatment of cardiomyopathy.<sup>13,14</sup> Results from a trial of vutrisiran are expected to become available in the next few months.<sup>15</sup> We heard from multiple stakeholders that the availability of tafamidis has resulted in

earlier detection of ATTR-CM and that this has caused a shift in the disease spectrum of patients enrolled in trials of these newer agents.

## Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient representatives, clinicians, researchers, and a manufacturer. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Discussions with patients emphasized that individuals with ATTR-CM often take years to receive the correct diagnosis even after being evaluated by cardiologists. Early symptoms commonly involve shortness of breath, fatigue, and sexual dysfunction. In some cases, individuals can be wrongly diagnosed with non-ATTR types of amyloid cardiomyopathy such as light chain amyloid cardiomyopathy; such patients have sometimes been inappropriately treated with chemotherapy. Patient groups have encouraged individuals being evaluated for ATTR-CM to receive care in specialized centers if possible.

Patients also report that the cost of tafamidis can be prohibitive. Some individuals prefer tafamidis but instead receive diflunisal, a non-steroidal anti-inflammatory drug (NSAID). Diflunisal is associated with improved survival and stability in clinical and echocardiographic parameters in observational data but has not been evaluated for ATTR-CM in a phase three randomized controlled trial and use is not supported in ATTR-CM in clinical guidelines.<sup>16,17</sup>

Clinical experts emphasized that although bone scintigraphy has been a very effective tool for earlier diagnosis, false positives are common when used in low-pretest probability individuals.

## Report Aim

This project will evaluate the health and economic outcomes of three disease modifying therapies for ATTR-CM. 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 ICER's [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 revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

### Populations

The population of focus for the review is adults with transthyretin amyloid cardiomyopathy (ATTR-CM).

Data permitting, we will evaluate the evidence for subpopulations defined by:

- ATTR-CM subtype (hereditary versus wild-type)
- NYHA functional class at baseline (class I or II, class III or IV)
- Race or ethnic group
- Sex or gender
- Age

### Interventions

The full list of interventions is as follows:

- (acoramidis) (BridgeBio Pharma)
- Vyndamax®/Vyndaqel® (tafamidis) (Pfizer Inc.)
- Amvuttra® (vutrisiran) (Alnylam Pharmaceuticals, Inc.)

## Comparators

Data permitting, we aim to compare interventions to each other and to no disease-specific treatment; this will be represented by the placebo arms of clinical trials in some circumstances, but we are aware that more recent trials have allowed some patients to receive open-label tafamidis.

## Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
  - Mortality
  - Cardiovascular-related hospitalization
  - Need for liver or heart-liver transplant
  - Change in exercise capacity (e.g., Six Minute Walk Distance)
  - Change in medication for heart failure (e.g., sodium glucose co-transporter inhibitors, mineralocorticoid receptor antagonists)
  - Health related quality of life (e.g., Transthyretin Amyloidosis – Quality of Life Questionnaire [ATTR-QOL], Kansas City Cardiomyopathy Questionnaire [KCCQ])
    - Reduction in cardiac (e.g., fatigue, shortness of breath), neuropathic (e.g., muscle weakness, sexual dysfunction), and gastrointestinal symptoms
  - Adverse events including:
    - Treatment-related mortality
    - Serious adverse events
    - Treatment-related discontinuation
- Other Outcomes
  - Changes in cardiac related biomarkers (e.g., NT-proBNP, serum transthyretin levels)
  - Changes in echocardiographic parameters (e.g., tissue Doppler imaging)
  - Changes in amyloid burden (e.g., extracellular volume measurement)

## Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

## Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

## Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities 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 general elements (i.e., not specific to a given disease) are listed in the table below.

**Table 1.2. Benefits Beyond Health and Special Ethical Priorities**

<b>Benefits Beyond Health and Special Ethical Priorities*</b>
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

\*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the [ICER Value Assessment Framework](#).

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

## Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on May 31, 2024. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest (acoramidis, tafamidis and vutrisiran) relative to no disease modifying therapy. The model structure will be based in part on a literature review of prior published models of ATTR-CM and other heart failure conditions; including the ATTR-CM models that examined the cost-effectiveness of systematic diagnostic screening and tafamidis use in the United States, United Kingdom, and Canada.<sup>7,18-21</sup> Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts and other indirect costs will be considered in a separate modified societal perspective analysis. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of improved functioning due to treatments

on productivity (patient and caregiver). The modified societal perspective analysis will be considered as a co-base case when direct data on indirect costs are available, the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per QALY, and/or when the result crosses the threshold of \$100,000-\$150,000 per QALY gained. The target population will include adults between the ages of 18 and 90 with an established diagnosis of transthyretin amyloid cardiomyopathy (hereditary or wild type) and clinical heart failure. The model may consist of health states based on the New York Heart Association (NYHA) functional classification or the Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom score along with a terminal state death.<sup>20,22</sup> A cohort of patients will transition between states during predetermined cycles (of six months) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using data from clinical trials for both the treatments and comparators.<sup>23-25</sup>

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of cardiovascular-related events avoided, time within different NYHA stages or average KCCQ symptom score over time, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained ([evLYG](#)). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons may be made between treatments. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per cardiovascular-related event avoided.

In separate analyses, we will explore the potential health care 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 economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices 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 [here](#).

## Identification of Low-Value Services

ICER includes 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 ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by ATTR-CM disease-modifying therapies (e.g., hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of ATTR-CM 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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