REPORT AT A GLANCE: TRANSTHYRETIN AMYLOID CARDIOMYOPATHY

OCTOBER 2024

KEY FINDINGS

Intervention	Comparator	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark
acoramidis (BridgeBio Pharma, Inc)	No disease specific treatment	B+ At least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit	N/A	$13,600 to $39,000 per year
tafamidis (Vyndamax®/Vyndaqel®, Pfizer Inc.)	No disease specific treatment	B+ At least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit	$268,000	$13,600 to $39,000 per year
vutrisiran (Amvuttra®, Alnylam Pharmaceuticals, Inc.)	No disease specific treatment or when added to tafamidis	A High certainty of a substantial net health benefit	N/A	Given the timing and availability of information about the effectiveness of the drug, the value of vutrisiran was not assessed.

"The independent panel confirmed the substantial clinical benefits of treating ATTR-CM with either a stabilizer or an RNA silencer, but also that the current price for tafamidis is much too high. The panel disagreed with ICER's conclusion that there is clear evidence for adding the RNA silencer vutrisiran to tafamidis in treating ATTR-CM, though the ICER research team stands by this conclusion. This adds even greater concerns around pricing, since combination therapy with drugs priced out of alignment with their clinical benefits will be extremely expensive and create strains in the health system."

– ICER's Chief Medical Officer, David Rind, MD

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THEMES AND RECOMMENDATIONS

- Federal and state policymakers should remove barriers to the use of telemedicine, including across state lines, so that individuals with ATTR-CM can access the most knowledgeable centers of excellence, regardless of geographic location.
- Clinical specialty societies should establish diagnostic cutoffs normalized for gender and/or body size both for screening for ATTR-CM in clinical practice and enrollment in clinical trials, to reduce failure to accurately diagnosis the condition in women and smaller patients.
- Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- Researchers and funding agencies should focus future research on efforts to establish the comparative effectiveness of tafamidis, acoramidis, and vutrisiran in similar populations.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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 the heart to stiffen. Eventually, the heart cannot fill properly, leading to shortness of breath, heart failure, arrhythmias, and death. Patients often have complex symptoms, because the shortness of breath can mimic other conditions and because amyloid fibrils can also deposit in other tissues causing other symptoms like pain and numbness. In that context, ATTR-CM patients are often diagnosed late in the disease course, after irreversible damage has occurred. Even after diagnosis, patients often struggle with access to treatments and knowledgeable subspecialists.

The true prevalence of ATTR-CM in the United States is unclear, given likely systematic underdiagnosis. It is likely at least 50,000 Americans have ATTR-CM, although by some estimates the prevalence could be much higher.

Prior to the approval of the oral TTR stabilizer tafamidis in 2019, patients with ATTR-CM were typically managed like other patients with heart failure with preserved ejection fraction, although some young patients would be treated with heart or heart-liver transplants. Another oral stabilizer, acoramidis, is under evaluation by the FDA with a PDUFA date of November 29, 2024. Efficacy data for treating ATTR-CM for an RNA silencing agent, vutrisiran, has recently been reported and the manufacturer has submitted a supplemental new drug application (sNDA). The RNA silencing agents reduce production of TTR proteins and have been approved for nerve damage in people with hereditary ATTR.

The trial that led to the approval of tafamidis demonstrated that tafamidis reduces mortality (HR 0.67) with survival curves diverging after approximately 18 months. Cardiovascular (CV)-related hospitalizations were also reduced, and declines in functional status and quality of life were slowed with minimal side effects.

The availability of tafamidis has led to earlier detection of ATTR-CM, and this has resulted in healthier patients being enrolled in subsequent trials of therapies. In the

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Clinical Analyses

primary trial of acoramidis, survival was numerically better at 30 months (81% vs. 74%), but this was not statistically significant. CV-related hospitalizations were reduced (RR 0.50) and declines in functional status and quality of life were slowed with minimal side effects. The lack of a statistically significant mortality benefit with acoramidis affects our judgment of both acoramidis and tafamidis in a contemporary population.

We have high certainty that tafamidis has substantial net health benefits in the population studied in its pivotal trial. While we recognize that, given the evidence base, clinicians and patients would be unwilling to wait for progression of disease before initiating therapy, this uncertainty about the magnitude of benefit is real. Thus, in a contemporary population, we have high certainty that treatment with tafamidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. ("B+") Similarly, in a contemporary population, we have high certainty that treatment with acoramidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. ("B+")

In its pivotal trial, vutrisiran reduced all-cause mortality at 33 to 36 months (16% vs. 21%; HR 0.69), achieved similar though statistically non-significant reductions in mortality in subgroups receiving or not receiving tafamidis. HELIOS-B recruited a contemporary population where 40% of participants were receiving tafamidis at baseline. Vutrisiran was well tolerated. As such, we have high certainty that treatment with vutrisiran, compared with no disease-specific therapy or when added to tafamidis, provides a substantial net health benefit. ("A")

Given the different populations studied, and the lack of additional data and analyses comparing the population in the HELIOS-B trial of vutrisiran with the population in the ATTRibute-CM trial of acoramidis or the ATTR-ACT trial of tafamidis, the evidence is currently insufficient ("I") to compare the net health benefits of the three agents.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

Based on the clinical evidence available, the economic modeling did not assume differences in treatment effects between the TTR stabilizers tafamidis and acoramidis. The modeling also assumed the tafamidis price for acoramidis. With these assumptions, a TTR stabilizer added to best supportive care resulted in improved health outcomes and higher costs compared to supportive care alone. Incremental cost-effectiveness ratios suggest that these therapies are unlikely to achieve commonly accepted cost-effectiveness thresholds.

The Health Benefit Price Benchmark (HBPB) for transthyretin stabilizing agents ranges from $13,600 to $39,000 annually. This would require discounts of 85% to 95% from the wholesale acquisition cost (WAC) for tafamidis. Because of the timing of new information on vutrisiran and lack of data needed for modeling, we did not perform economic modeling of this agent.

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Economic Analyses

POTENTIAL BUDGET IMPACT

A potential budget impact analysis was not conducted for transthyretin stabilizing agents. Our model analysis plan expected to compare acoramidis to the management of ATTR-CM without treatment. We noted in our analysis plan that if the relative effectiveness and price of acoramidis compared to tafamidis is similar, the budget impact of acoramidis replacing tafamidis is likely to be minimal. There was insufficient data to differentiate between acoramidis and tafamidis in the cost-effectiveness analysis, and as such, the treatment efficacy and cost of both agents were assumed to be the same. It is expected that acoramidis will compete with tafamidis for market share among the same eligible patient population, so under conditions of the same efficacy and cost, there would be no impact on payer budgets.

Public Meeting Deliberations

VOTING RESULTS

ICER's Public Meeting: Voting Results on Clinical Effectiveness and Benefits Beyond Health

ICER assessed, and the independent appraisal committee voted on the evidence for adults with ATTR-CM:

- A majority of panelists (14-0) found that current evidence is **adequate** to demonstrate a net health benefit for tafamidis when compared to no disease-specific treatment.
- A majority of panelists (15-0) found that current evidence is **adequate** to demonstrate a net health benefit for acoramidis when compared to no disease-specific treatment.
- A majority of panelists (14-0) found that current evidence is **adequate** to demonstrate a net health benefit for vutrisiran when compared to no disease-specific treatment.
- A majority of panelists (15-0) found that current evidence is **not adequate** to demonstrate a net health benefit for vutrisiran added to tafamidis when compared to tafamidis alone.
- A majority of panelists (15-0) found that current evidence is **not adequate** to distinguish a net health benefit among the interventions when used as monotherapy (tafamidis, acoramidis, vutrisiran).

Panel members also weighed potential benefits and disadvantages beyond the direct health effects, and weighed special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.
- This condition is of substantial relevance for

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Public Meeting Deliberations

people from a racial/ethnic group that have not been equitably served by the healthcare system.

- The TTR stabilizers are likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.

ICER's Virtual Public Meeting: Voting Results on Long-Term Value for Money

Tafamidis has been approved by the FDA for ATTR-CM and has a list price of approximately $268,000 per year. Acoramidis and vutrisiran have not yet been approved by the FDA for ATTR-CM, and the manufacturers have not announced US prices for each therapy if approved.

For adults with ATTR-CM:

- A majority of panelists (13) found at the current pricing, tafamidis compared to no disease-specific treatment represents a **"low"** long-term value for money. Two panelists voted that the therapy represented an "intermediate" long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.

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