Disease Modifying Therapies for the Treatment of ATTR-CM
Response to Public Comments on Draft Evidence Report

September 5th, 2024

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#	Comment	Response/Integration
Manufacturers		
BridgeBio		
1.	BridgeBio has reviewed the draft report (July 17, 2024) of ICER's review of treatments including acoramidis, a next-generation transthyretin (TTR) stabilizer in development for the treatment of transthyretin amyloidosis cardiomyopathy (ATTR-CM). While diagnosis rates have improved in recent years, a substantial unmet need persists in ATTR-CM due to the incomplete TTR stabilization associated with currently approved therapeutic options.	We acknowledge in the report that some clinical experts believe that TTR stabilization will be correlated with better clinical outcomes. As we also note, other clinical experts disagree that TTR stabilization will be correlated with better clinical outcomes.
2.	Based on phase 3 trial results, and if approved by the FDA: • Acoramidis has the potential to extend survival and to reduce healthcare resource use, including cardiovascular-related hospitalizations. The ICER draft evidence report notes that, in the ATTRibute-CM trial, acoramidis resulted in a reduction in the risk of cardiovascular-related hospitalization vs placebo (relative risk 0.50, 95% CI 0.36 to 0.70). This benefit is rapid: in ATTRibute-CM, the Kaplan-Meier curve for the composite of first cardiovascular-related hospitalizations and cardiovascular-related mortality begin to separate at Month 3 and progressively diverged through Month 30. BridgeBio considers reduction in hospitalization frequency to be a patient-, caregiver-, healthcare system-, and payer-relevant benefit, as hospitalization is costly, puts patients at risk of infection and other complications, presents additional caregiver burden, and impacts patient quality of life. • Acoramidis is expected to represent a new treatment option for ATTR-CM, which currently has only one approved disease-modifying treatment. As an alternative to a currently approved product, acoramidis is not expected to have a substantial impact on payer budgets. BridgeBio advocates for access to all approved treatment options for ATTR-CM, so that patients and providers can consider the most appropriate option for the individual over the course of treatment. With our shared goal of supporting patients, caregivers, and clinicians through greater awareness of—and expanded treatment options for—ATTR-CM, BridgeBio offers the following comments on the draft evidence report.	We agree that reduction in hospitalizations is a patient-important outcome and it appears as such in our PICOTS. The budget impact of a therapy is distinct from a fair price for that therapy. That tafamidis may already be priced far above a cost-effective price is not a reason to suggest price reductions for tafamidis but not a fair price for acoramidis.

3.	**Economic model considerations** BridgeBio was unable to replicate the results of the model and therefore would welcome additional details on the methods and inputs, including validation of the inputs, used in the economic model described in the ICER report. Particularly, the quality-adjusted life year (QALY) gain for disease-modifying treatment vs best supportive care in the model is 0.3 QALYs, which is unexpectedly low, given that the clinical benefit rating is B+. Recognizing that the analyses are based primarily on tafamidis, not acoramidis, data, we call attention to the much larger QALY gains estimated in other economic models of tafamidis in ATTR-CM: • **Published CEAs and disease simulations of tafamidis in ATTR-CM**: Incremental QALYs with treatment range from 1.29 to 2.55 to 3.29. • **Publicly available HTA submissions of tafamidis in ATTR-CM:** Incremental QALYs with treatment range from 1.45 (HAS) to 1.97 (PBAC) and 2.02 (CADTH-preferred base case). Given that the ICER estimate utilizes NYHA transition probabilities based on the HAS submission, the 80% reduction in estimated incremental QALYs compared to the HAS estimate is particularly striking. BridgeBio would welcome additional transparency on the model's approach to mortality, particularly the calibration in the base case, and the hazard ratios used for Scenario Analysis 2, to better understand the model result.	We agree that the model results for the draft report appeared to be different from previously published reports. We therefore undertook a thorough evaluation of the model inputs and calculations. We also validated model findings against other published studies. We identified an error in the model that was significantly affecting the QALY calculations, over-counting the impact of hospitalizations on QALYs. Compared with published studies, we also determined that life-expectancy did not match what might be expected. We identified that for patients on treatment, rather than attempting to fit a single curve to survival data, a two-part survival curve better approximated observed survival. These issues with the model were corrected and result in more appropriate estimates for QALYs and LYs, resulting in QALYs that are closer to those in the CADTH report and very closely matching observed life expectancy data. Additional changes were made to the model utilities to address these concerns (see comments above). As part of ICER's efforts to acknowledge the importance of model transparency, we offered to share the model with relevant manufacturers. We encourage all manufacturers to participate in the model transparency program, and participation in this initiative would have been an opportunity for BridgeBio to review the details of the modeling approach used for mortality. We have revised our report to reflect our modeling updates since the draft report, and where possible, have identified opportunities throughout the report to improve clarity in our descriptions of methods used.
4.	**Association of improved clinical outcomes with greater TTR stabilization in ATTR-CM** The draft evidence report recognizes the benefits of disease-modifying treatment for ATTR-CM and assumes	We acknowledge the evidence for higher TTR stabilization with acoramidis relative to tafamidis and discuss this in the report. We think that any definitive analysis of the comparative effectiveness of acoramidis

	improved health outcomes compared to supportive care alone, without attempting to compare the efficacy of the three treatments. BridgeBio agrees that disease-modifying treatment benefits patients, and that it is not feasible to compare acoramidis, tafamidis, and vutrisiran based on the publicly available clinical data, due to differences in baseline patient characteristics and trial design. BridgeBio does, however, consider acoramidis to offer unique benefits based on its higher level of TTR stabilization compared to existing options. Currently available TTR stabilizers are associated with incomplete stabilization that ranges from 32% to 71% according to ATTR-CM genotype. In laboratory tests at trough and peak concentrations comparable to 80 mg doses, tafamidis provided incomplete stabilization of TTR (<67%) with between 34% and 52% binding site occupancy, whereas acoramidis was found to stabilize completely with 100% binding site occupancy. Similar results for acoramidis have been observed in vivo: in patients with ATTR-CM, acoramidis achieved ≥90% TTR stabilization and increased serum TTR levels. TTR stabilization has been associated with improved outcomes: an early increase in serum TTR during acoramidis treatment has been associated with lower cardiovascular mortality and cardiovascular hospitalization. Moreover, an early increase in serum TTR level during acoramidis treatment is an independent predictor of improved survival. Near-complete TTR stabilization with acoramidis therefore represents an important step forward in targeted treatment of ATTR-CM.	relative to tafamidis should compare patient-important clinical outcomes rather than the surrogate outcome of TTR stabilization. Ideally this would involve prospective randomization but at a minimum should involve rigorous methods for comparative effectiveness research with observational data (given the potential for selection bias).
5.	BridgeBio has concerns regarding statements on serum TTR in the draft report. The report suggests that the difference in serum TTR levels observed at Month 30 between the acoramidis and placebo-to-tafamidis arms in ATTRibute-CM may be due to the placebo group having a year without disease-modifying treatment before crossing over to tafamidis. However, the two groups had similar baseline serum TTR levels, and treatment with acoramidis led to a sharp increase in serum TTR within the first 28 days of treatment. A sharp increase in serum TTR did not occur in the weeks following crossover to tafamidis. This suggests that acoramidis, but not tafamidis, leads to a rapid and notable increase in serum TTR levels upon treatment initiation.	We acknowledge that before randomization, the group arms had similar TTR levels. The concern we have about prolonged time without treatment is different – the acoramidis group had more time on a stabilizer compared with the group that was only on tafamidis after some time receiving placebo. If you have data on the differences in TTR levels after starting each drug in the same trial and study population, we would welcome the opportunity to review those data. Overall, in our discussions with clinical experts, there were disagreements about the extent to which serum TTR levels would be correlated with improved clinical outcomes. We highlight this point in the report.

6.	Acoramidis represents an important new orally administered option to address the persistent unmet need in ATTR-CM. BridgeBio supports providing patients and their providers with the opportunity to choose treatments based on their needs and preferences. We recommend that any health economic review of acoramidis consider its clinical benefits and the value of patient choice. We further recommend that the review should be revisited and updated as real-world data on all approved ATTR-CM treatments as they become available in the coming years. Thank you very much for your consideration.	Thank you for these comments. We agree that choice can be an important consideration, particularly when therapies have different timing of benefits and harms. We also share your interest in additional data, particularly comparing treatments.
Pfizer		
1.	**Comparative Clinical Evidence** ICER conducted a systematic literature review to assess the comparative clinical effectiveness of three disease-modifying therapies (acoramidis, tafamidis, and vutrisiran) for adults with ATTR-CM. The review focused on key outcomes that matter to patients, such as mortality, hospitalization, functional capacity, and quality of life. Tafamidis, the first-in-class medication for ATTR-CM patients, demonstrated statistically significant improvements in key outcomes identified by ICER in the ATTR-ACT study, the largest and longest randomized controlled trial in this disease area. To this date, tafamidis is the only FDA product approved for the treatment of the cardiomyopathy of wild type or hereditary ATTR-CM in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Since the regulatory approval of tafamidis, the disease course of ATTR-CM has changed from untreatable to manageable. Tafamidis is now recognized as a conventional treatment and is recommended in guidelines worldwide. Similarly, a 2023 consensus statement by the ACC acknowledges alternative therapies exist but emphasizes that tafamidis remains as the "first-line agent" for ATTR-CM wild type and hereditary forms with NYHA I to III symptoms due to its current approval status, giving tafamidis a Class 1 recommendation based on its evidence in the 2022 AHA/ACC/HFSA Heart Failure Guidelines. Advances in research, disease education, and the availability of tafamidis have increased awareness and screening efforts for ATTR-CM, resulting in more patients being diagnosed at an earlier stage. Subgroup analysis in the ATTR-ACT study for patients in the early stages of their disease (i.e., NYHA Class I and II) show improved outcomes for patients treated with tafamidis. In this subgroup, results show a consistent and significant benefit for patients	We appreciate these important comments. We recognize this is a difficult issue given the early efficacy demonstrated in ATTR-ACT, the class 1 recommendation in the heart failure guidelines, and lack of equipoise afterwards. Although we appreciate the additional information from the THAOS registry, we note the important roles of treatment selection bias in THAOS as well as immortal time bias in this observational registry. We also note that there is not a dedicated randomized comparison of tafamidis against placebo in contemporary patients with current diagnostic techniques. We have included some of the survival data that you cite here from THAOS in the main evidence report. We also acknowledge the class 1 recommendation in clinical guidelines that you point out. We have updated the Report with published evidence from HELIOS-B and also updated the evidence rating for vutrisiran.

	receiving tafamidis in survival, CV related hospitalizations, and quality of life. Additionally, the long-term extension for ATTR-ACT (median follow-up of 58.5 months) reported 5-year survival rates in the same NYHA Class I or II population of 61.4% with continuous tafamidis treatment and 40.3% in the placebo to tafamidis group- reinforcing positive outcomes in early disease. These results are consistent with those from the real-world Transthyretin Amyloidosis Outcomes Survey (THAOS) study which includes a subset of patients with ATTR-CM that are representative of a contemporary population (i.e., higher proportion of NYHA I-II patients and a lower median NT-proBNP concentration). Among THAOS, ATTR-CM participants enrolled from 2019 onwards (n = 670), 80mg/61mg tafamidis-treated patients showed 30- and 42-month survival rates of 86.3% (95% CI 80.4–90.5). In contrast, untreated patients had lower survival rates of 77.2% (95% CI 69.8–83.1) at 30 months and 67.3% (95% CI 56.9–75.8) at 42 months. Tafamidis was well tolerated with a favorable safety profile without new safety signals. Overall, the evidence supporting the clinical effectiveness of tafamidis in patients with ATTR-CM, including the contemporary population, is extensive, as it includes the pivotal ATTR-ACT clinical trial, its LTE, and the real-world THAOS study. ICER's Evidence Rating Matrix aims to reflect the magnitude of difference (i.e., net health benefit) between tafamidis and no disease-specific therapy, and the level of certainty in the best point estimate of net health benefit. ICER concluded that there is a high certainty that tafamidis provides a substantial net health benefit in the population assessed in ATTR-ACT, but only a moderate certainty of a substantial net health benefit in a contemporary population (B+). This same rating was given to acoramidis and to vutrisiran. However, unlike tafamidis, acoramidis did not show a mortality benefit in its ATTRibute-CM trial, and mortality should be considered as a main outcome when evaluating the difference between a "small" and "substantial" net health benefit. Additionally, while primary data from a press release is available for the HELIOS-B trial that indicates a mortality benefit for patients treated with vutrisiran, this data is not yet published in a peer reviewed publication. Considering that major changes to follow-up time and outcomes were recently made to the HELIOS-B trial design, it is necessary that a peer-reviewed publication be published before ICER can make a proper evaluation of the certainty of the evidence.	

	On a webinar entitled "ICER Early Insights Webinar Series: Transthyretin Amyloid Cardiomyopathy" ICER noted that if tafamidis was being evaluated in the original trial population it would score an A, but there is less certainty in the contemporary population of ATTR-CM. Pfizer agrees that the availability of tafamidis has dramatically changed patient outcomes in this disease area and has led to earlier diagnosis and better prognosis for people with ATTR-CM. However, the evidence of tafamidis in less severe patients is just as robust as in the whole population of the ATTR-ACT trial. Pre-specified subgroup analyses of NYHA I/II subgroup demonstrated similarly robust benefits for survival in both the original trial (HR 0.568 [0.358,0.902], $P < 0.01$) and the long-term follow-up (HR 0.56 [0.38,0.82], $P = 0.003$). Contemporary analyses in the THAOS study further support this, with 80/61mg tafamidis providing an extended lifespan compared with no tafamidis treatment in patients treated since 2019 (tafamidis survival at 42 months = 86.3% [80.4,90.5] vs untreated survival at 42 months = 67.3% [56.9,75.8]). Thus, there is no rationale to claim that there is a difference in level of certainty of the benefit of tafamidis in the contemporary ATTR-CM population compared with when the ATTR-ACT trial was run.	
2.	**Comparative Clinical Evidence** Action: Tafamidis is the only FDA-approved disease modifying therapy in ATTR-CM that has shown a sustained net health benefit through both extensive clinical trial data and real-world evidence, impacting key patient outcomes across all stages of NYHA classifications, particularly in NYHA Class I and II. We would therefore recommend that ICER's evidence rating for tafamidis should reflect the totality and depth of peer-reviewed evidence, consistent with the rigor of evidence-based guidelines and provide tafamidis with a higher evidence rating relative to the other therapies in this assessment. The rating should be an A given that ICER noted this would be the rating in the original trial population, and the evidence for tafamidis's efficacy and safety are similarly robust in patients diagnosed in earlier stages of the disease (i.e., those with NYHA I/II) representative of a contemporary population.	We are impressed by the data overall for efficacy of tafamidis and as such assigned a strong B+ rating. Of note, one of the specific differences between B+ and A is the level of certainty in the magnitude of the effect; in this case, the extrapolatability of ATTR-ACT to contemporary practice creates more uncertainty about the magnitude of benefit. We also appreciate and acknowledge the class I rating in clinical guidelines in the report. Overall, the relative difference in evidence ratings of different therapies versus no therapy should not be interpreted as our assessment of the comparative effectiveness of any 2 therapies. Although there are different arguments for the different treatments that we summarize in the report, there are not randomized comparisons of ATTR-CM therapies against one another and we highlight the lack of evidence of these treatments against one another.

		Of note, the unadjusted mortality of the tafamidis arm in ATTR-ACT was higher than in the placebo arm of ATTRibute-CM (testing acoramidis), highlighting that these trials were conducted in very different populations. This creates uncertainty about the magnitude of the treatment effect in a contemporary population.
3.	**Long-Term Cost Effectiveness- Survival Extrapolation** ICER developed a *de novo* decision analytic model to estimate the cost-effectiveness of the class of transthyretin stabilizing agents compared to best supportive care (BSC) alone for patients with ATTR-CM. The model was informed by key clinical trials and prior relevant economic models. Overall, the incremental cost per QALY gain predicted by ICER was a value of $1,896,000, nearly double that of the value reported in a prior economic model evaluating tafamidis from a US perspective reporting a value of $880,000 ($697,000-$1,564,000) for tafamidis over usual care. Relative to existing published models, ICER predicted a small incremental QALY value (0.3 in the report and 0.74 in the webinar) compared with other economic models reporting values of 1.29 and the undiscounted value of 3.29. Similarly, the undiscounted LYs predicted by ICER's model (4.0 in the original report, 4.57 in the updated webinar) are substantially lower when comparing to other model values of 5.43 and 6.47, resulting in incremental LYs gains of 1.00, 1.97, and 3.88, respectively. This is misleading considering that ICER has chosen to model the disease progression in the ATTRibute-CM population who are less severe and more likely to have a better prognosis than the ATTR-ACT trial population used by all of the existing reports.	We agree that the model results for the draft report appeared to be different from previously published reports. We therefore undertook a thorough evaluation of the model inputs and calculations. We also validated model findings against other published studies. We identified an error in the model that was significantly affecting the QALY calculations by over-counting the impact of hospitalizations on QALYs. Compared with published studies, we also determined that life-expectancy did not match what might be expected. We identified that for patients on treatment, rather than attempting to fit a single curve to survival data, a two-part survival curve better approximated observed survival. These issues with the model were corrected and result in more appropriate estimates for QALYs and LYs, resulting in QALYs that are closer to those in the French technology assessment report and very closely matching observed life expectancy data.
4.	**Long-Term Cost Effectiveness- Survival Extrapolation** Furthermore, in contrast to existing published models in this space which used parametric survival extrapolation to assess transition to mortality, ICER chose to predict survival using hazard ratios for both ATTR-CM mortality and TTR stabilizer efficacy applied to general population mortality curves. This approach has a significant limitation. By using a single hazard ratio approach, ICER is assuming that the hazard of mortality between TTR stabilizing agents and standard of care is constant. However, published proportional hazards testing through Schoenfeld residuals	We reviewed the modeling approach for estimating mortality and observed that the hazard ratio for those on treatment did appear to change over time, initially matching the placebo group and separating at 18 months. Therefore, for treatment, we split the observation period into two periods, estimating the hazard ratio (HR) for the first 18 month period as being similar to placebo and then estimated a second HR for after 18 months. The resulting HRs closely

	demonstrated that the proportional hazards assumption is violated (particularly in the NYHA I/II subgroup most representative of a contemporary population), which is why the Rozenbaum model used independently fit survival extrapolation to both the tafamidis and standard of care arms. ICER notes that applying pure survival extrapolation may underpredict based on general population mortality (GPM). However, we note that several recent papers have explored approaches incorporating GPM based on published Kaplan-Meier data with no individual patient data available. The internal additive hazards approach has been shown in some applications to outperform no GPM adjustment and applying proportional hazards for ACM vs GPM hazards (ICER's approach). This approach would yield valid extrapolations that don't rely on assuming proportional hazards for data where this assumption is violated.	resembled survival in the tafamidis open-label extension study.
5.	**Long-Term Cost Effectiveness- Survival Extrapolation** Action: Given the established discordance in LY prediction compared with previous evaluations, and the application of a hazard ratio to data where proportional hazards do not hold, reconsidering the existing approach to model mortality should be undertaken. As an alternative, a parametric survival extrapolation method such as the internal additive hazards approach or time-varying hazard ratios would allow rigor and consistency with the currently available data.	We have updated the approach to modeling survival as described above. The estimated LY gain is now larger and is consistent with what is observed in the initial tafamidis control trial.
6.	**Long-Term Cost Effectiveness- Utilities** Beyond the underprediction of life-years, the difference in QALYs predicted by ICER is notably lower. The average utility per patient predicted by the model is unrealistically low. A raw conversion between LYs and QALYs from ICER's model suggest an average utility per patient of roughly 0.43 in the report and 0.56 in the webinar values (undiscounted in the report, uncertain of discounting application in the webinar reported values) compared to 0.80 (undiscounted) and 0.72 (discounted) in recent economic models. This suggests that ICER's model is underestimating the average utility per patient, especially considering that patients spend most of their LYs in NYHA II/III with utilities ranging from 0.633-0.729. This was noted by David Rind on the ICER webinar: "*I have at least some concerns that that difference between the QALY and evLY requires us to look a little bit more at the model*". This is almost certainly due to a double-counting issue, given that ICER evaluated hospital-related disutilities as an add-on to health state utilities from	We identified an error in the way disutilities were being applied to hospitalizations. The error now has been corrected. In addition, using treatment-specific health-state utilities appeared problematic, as they were not statistically different and appeared to be counterintuitive for patients with Class IV heart failure (disadvantaging treatments). We therefore updated health state utilities, applying the same averaged utilities to both treatment and placebo, and maintained the disutilities for hospitalizations.

	the ATTR-ACT trial. Measurements of health state utilities in the ATTR-ACT trial already reflect the hospitalization rates within ATTR-ACT which is why previous HTA evaluations in this disease area have accepted no disutilities for these events. By applying both health state utilities that reflect a given hospitalization rate and an additive disutility for hospitalization rates, ICER is substantially under-valuing the quality of life and patient experience for people with ATTR-CM. **Long-Term Cost Effectiveness- Utilities** Action: Given the improbably low utilities generated by ICER's evaluation, the approach to utilities in this model should be reconsidered. As health state utilities from the ATTR-ACT trial already capture the impact of hospitalization on quality of life, the hospitalization-related disutilities should be set to zero. Alternatively, if ICER wishes to evaluate hospitalization rates that differ from ATTR-ACT, only the utility impact of differences in hospitalization rates should be applied.	
7.	While ICER's efforts to conduct an assessment on disease modifying therapies for ATTR-CM are certainly appreciated, it is important to remind stakeholders that conventional cost-effectiveness approaches that use the QALY poses some challenges in rare diseases like ATTR-CM. The use of QALYs can bias the assessment of value, particularly against elderly populations who have a shorter life expectancy and less time to benefit from treatment, which can, in turn, have serious negative implications to patients having access to efficacious rare disease drugs. To conclude, we firmly believe in the clinical effectiveness and value of tafamidis as the standard of care for ATTR-CM. Thank you for the opportunity to comment on the ICER Draft Evidence Report. We look forward to reading the final report and participating in the upcoming public meeting.	As we discuss in the report, there is known systematic underdiagnosis of ATTR-CM. ATTR-CM is sufficiently common that we believe standard cost-effectiveness approaches are appropriate. In fact, it may be so common as to create budget impact strains at cost-effective prices. While there are situations in which it is important to focus on evLYs when examining therapies that extend life, we do not believe (as in this case) that QALYs generate a bias against any treatment that, when used in populations with competing risks for mortality, produces benefits that can only be accrued for those who survive. Moreover, we note that general arguments suggesting that the QALY systematically discriminates against the elderly, while long held, have not stood up to empirical inquiry. For example, a recent analysis of nearly 5,000 QALY-based evaluations indicated no significant differences in cost-effectiveness

		conclusions for populations <65 years of age vs. 65 or older.[1]

#	Comment	Response/Integration
Patient/Patient Groups		
Amyloidosis Research Consortium (ARC)		
1.	In recent years, several advances have been made in the screening and diagnosis of patients for transthyretin amyloid cardiomyopathy (ATTR-CM). Patients with suspected ATTR-CM can now be effectively screened and diagnosed using a combination of non-invasive tests (echocardiography, cardiac magnetic resonance, bone avid tracers with cardiac scintigraphy), which has reduced the need for biopsies. There is also an increasing awareness of early indications of the disease among healthcare professionals, such as the presence of carpal tunnel disease. However, the diagnostic odyssey that patients and caregivers undergo before receiving an accurate diagnosis of ATTR-CM, either wild type (ATTRwt-CM) or hereditary (ATTRv-CM), is still long and challenging. We have extensively examined the ATTR patient diagnostic journey and associated burden through our Amyloidosis Research Consortium (ARC) annual community surveys of amyloidosis patients and caregivers. ATTR amyloidosis is a multi-systemic disease that can present with a wide array of non-specific symptoms. Patients are often required to see multiple healthcare professionals requiring numerous referrals before receiving a diagnosis. A recent review conducted by Rosenbaum, et al., also found the average delays to diagnosis for either ATTRwt-CM and ATTRv-CM are 6 years, on average. Misdiagnosis is also common, with patients undergoing unnecessary procedures and receiving inappropriate treatments as a result. As noted by ICER, patients with ATTR-CM are often only diagnosed after advanced disease progression.	We have now included the specific data and citation you provide here in the main report in additional discussion of delay to diagnosis.
2.	While progress has been made towards earlier detection and diagnosis of ATTR-CM, which is resulting in less advanced disease progression and lower mortality rates among an increasing number of newly diagnosed patients (e.g., a “left shift” in the disease paradigm), many patients and caregivers still face several hurdles and significant burden in receiving timely and appropriate care, including access to appropriate disease-modifying treatments. Participants in ARC’s patient programs and research initiatives have given voice to the frustration associated with these delays including the extensive burden that is placed on family members and caregivers, along with the impact on their health-related quality of life associated with delayed treatment. In addition to the significant impact on the patient’s daily life, these diagnostic delays present an	Thank you for these thoughtful comments.

	increased mortality risk, as ATTR-CM is a progressive condition with a high mortality rate if left untreated.	
3.	There is an unmet patient need for additional supportive therapies and disease modifying treatment options for effective management of ATTR-CM. Tafamidis, a TTR stabilizer, is currently the only FDA approved treatment for ATTR-CM. Patients and healthcare providers will greatly benefit from having more treatment options available for ATTR-CM. New treatments are on the horizon, including expected FDA approvals for acoramidis and vutrisiran in the near future. As more treatments become available, healthcare providers, patients, and payers will become increasingly reliant on evidence generated by comparative effectiveness research (CER) studies to help determine which treatments will likely work best for which patients, and under which circumstances. Patients and caregivers will benefit from the opportunity to participate in shared decision-making with their healthcare providers to determine treatment selection. Currently, there is a lack of CER data to help inform healthcare provider and patient's treatment choices for ATTR-CM. There is also a critical need for real-world evidence (RWE) to understand the impact of earlier diagnosis, differences in genetic variances of the disease, heterogeneity of treatment effects, and other clinical factors associated with patient outcomes, including more contemporary estimates of disease progression and mortality.	We agree with these thoughtful comments and discuss some of these issues in the report.
4.	ARC developed the Transthyretin Amyloidosis Quality of Life (ATTR-QOL) Questionnaire to understand patient perceived quality of life in a changing diagnostic and treatment landscape, which has been increasingly adopted for use in clinical trials, observational research studies, and clinical practice settings however insights into ATTR-CM patient's treatment preferences and their expected willingness to pay are currently lacking. It will also be crucial to understand appropriate treatment approaches for ATTR-CM patients with other organ involvement. In 2023, ARC conducted a survey of amyloidosis patients which found that among 315 respondents with ATTR-CM, over half (n=151) reported additional nervous and/or gastrointestinal involvement (GI). Patients with multi-organ involvement reported higher frequency and/or severity of cardiac symptoms compared to patients with isolated cardiac symptoms, which suggests that quality of life of ATTR-CM patients is worse for those with multi-systemic disease, particularly those with cardiac and GI involvement, compared to those with just cardiac involvement.	See comment above.

5.	As noted by ICER, the comparative analysis included in the ATTR-CM report was restricted to currently available pivotal trial data, surrogate outcomes of post-treatment TTR serum levels, and a single center study comparing long term outcomes of patients treated with tafamidis or acoramidis, which is a limitation. Key stakeholders, including ICER, life sciences researchers, pharmaceutical manufacturers, payers, healthcare providers, patient organizations, and ATTR-CM patients and their caregivers will benefit from access to more comprehensive data gathered through CER and RWE studies, as well as prospective studies designed to capture much-needed patient and caregiver perspectives, to help determine the benefit of new and emerging treatments with the shared goal of improving patient outcomes.	We agree that these types of studies are sorely needed.

#	Comment	Response/Integration
Other		
Partnership to Improve Patient Care (PIPC)		
1.	**ICER's models continue to oversimplify complex diseases in a manner that may misrepresent treatment effectiveness.** ICER's model categorizes patients into broad health states, missing marginal but meaningful improvements and likely underestimating the value of treatment. As PIPC has made clear in the past, in cost-effectiveness modeling it is problematic to oversimply a disease by using a model with too few health states. If treatment value is represented by movement of patients from a worse state to a better state, and too few states are identified or too crudely defined, then the number of people transitioning between states may appear to be low despite meaningful improvements within the overly broad health state, potentially underestimating the effectiveness of the treatment. ICER's model assumes a similar distribution of severity within states as across states. People who remain in the state they started in at the end of a cycle may have a marginal improvement in outcomes that is not reflected in ICER's conclusions because they have not transitioned to the next defined health state. The model does not differentiate outcomes for people receiving treatment who improve but do not transition to a different health state from those who do not receive the treatment at all. Yet, marginal improvements can be vitally important to the patients in question and significantly improve their quality of life. When a model simplifies a complex disease down to a transition between three health states, as ICER's does, it is likely missing these marginal improvements and not capturing accurate treatment value. This type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of treatment effects.	There were no statistically significant differences observed between treatment and placebo for utility in patients within NYHA classes. The data do not support the claim being made here. Regarding the model oversimplifying the condition, we have conducted a comprehensive systematic review of past models, including those developed by manufacturers with access to detailed clinical trial data. The model was developed considering the benefits and limitations of all published (and often peer-reviewed) models. Further, the model results were validated against tafamidis clinical trial data. We believe our model appropriately estimates the costs and benefits of treatment so as to suggest fair pricing for these agents.
2.	**ICER's report references the system effect of introducing treatment for transthyretin amyloid cardiomyopathy, but it does not include this in its modeling.** ICER's report makes note that the very existence of the first disease modifying treatment for ATTR-CM has led to an improved diagnosis rate. Early detection of disease leads to improved care, an element of value accrued to all ATTR-CM patients as the result of development of DMTs that is realized regardless of whether the patient is on the drug.	The implication seems to be that a therapy should command a higher price if the existence of a treatment creates a reason for detection of disease. Since the only benefit of early detection is treatment with the new therapy, and the therapy will benefit from greater sales as new cases are detected, this does not seem appropriate.

	This systems effect of treatments is something that has been discussed consistently in research literature Yet, this indirect marginal benefit that accrues to all ATTR-CM patients is not incorporated into standard cost-effectiveness modeling. Contrary to this element of value, ICER tries to make the case that *because* patients are now being diagnosed earlier and at less severe stages of disease, the net benefit of treatment could in fact be smaller than was seen in the trials for tafamidis, precisely because at the time these trials were conducted, the mean severity of a newly diagnosed patient was much higher. It is obvious that this was the case because no treatment existed, and doctors were not actively diagnosing ATTR-CM as often. <u>We are very concerned that this type of overly simplistic value assessment methodology risks actively disincentivizing innovation to the detriment of patients.</u> The fact that a new treatment has led to early diagnosis, better care and decreased severity of disease is evidence of its value for patients.	We would appreciate additional clarity on PIPC's suggested approach. For instance, would it then be the case that a second therapy, as such acoramidis, should be priced substantially less than tafamidis since it was not responsible for the increase in disease detection?
3.	PIPC reiterates past comments and encourages ICER to evolve its value assessment methodology to include a wider, more complete, set of benefits so that cost-effectiveness models reflect the full scope of factors that represent value of new therapies for patients, health care providers and society at large. Academically many of these approaches have been widely accepted. For example, the elements of value of innovation, risk-adjustment and system effects all apply here. Therefore, PIPC encourages ICER to rethink its modeling to include these elements.	ICER reports include a detailed review of the existing literature as well as input from stakeholders highlighting benefits beyond health and special ethical priorities offered by the intervention that should be considered by policymakers. There are important ethical implications of expanding the dimensions of value quantitatively assessed that we detail in Section 3.5 of our Value Assessment Framework. We also note that we have publicly committed to exploring how to incorporate some novel approaches in a way that does not have unintended consequences for patient costs and access. When and if those approaches are ready for implementation, we will be transparent about how and when it is appropriate to incorporate those other dimensions of value quantitatively.
4.	**ICER uses utilities derived from randomized controlled trial (RCT) data.** There are many limitations to using utility data derived solely from RCT settings. RCT populations are generally much healthier than real-world disease-specific populations. There are always explicit and implicit exclusion criteria for recruitment into trial settings, including age, the existence of co-morbidities and levels of healthcare access	We agree that it is important to use the best available evidence to populate model inputs. We conducted a thorough literature review and sent a detailed data request to manufacturers of tafamidis and acoramidis. We determined that the utilities derived from the tafamidis clinical trial were the best available estimates for this population.

	and utilization, that make RCT populations rarely representative of real-world populations of need. Additionally, utilities in RCTs tend to be inflated compared to non-RCT samples of patients as patients in RCTs receive greater care and attention from healthcare professionals, which improve quality of life measures, even those not directly correlated to receiving the treatment. These discrepancies in utilities generated in RCTs versus real-world populations is well documented in research literature.	
5.	**ICER should reflect the heterogeneity of ATTR-CM subtypes either directly in the model or in parallel scenarios analyses**. The model is constructed for a single population of ATTR-CM patients. There is a subtype of ATTR-CM patients who will also have comorbid ATTR-PN (polyneuropathy), which makes the condition significantly more burdensome. Given this increased burden, it would be likely that disease-modifying therapies (DMTs) would be more beneficial for this population and therefore significantly more cost-effective. ICER's model would be more accurate by running scenario analyses for those who have both conditions.	We are not aware of any data to support an assessment of ATTR-CM subtypes in the model. We agree it is possible that treatment for patients with ATTR-PN could be similar.
6.	**ICER continues to use the discriminatory QALY and other one-size fits all metrics.** Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, older adults and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments. The recent nondiscrimination regulations governing Section 504 of the Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance.	Thank you for this comment. We invite you to review our Value Assessment Framework for a detailed overview of the different methods and concepts we use in our reviews: https://icer.org/ourapproach/methods-process/valueassessment-framework/ The quality-adjusted life year (QALY) is an established academic standard for measuring how well all different kinds of medical treatments lengthen and/or improve patients' lives, and therefore the metric has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. If evidence shows that a treatment helps lengthen life or improve quality of life, these benefits are comprehensively summed up to calculate how many additional QALYs the treatment provides, and this added health benefit is then compared to the added health benefit of other treatments for the same patient population. Concerns have been

		raised that the QALY may theoretically undervalue treatments for disabled or severely ill populations in comparison to healthier individuals. As an alternative, ICER developed the equal-value life year (evLY) measure, which values the additional years of life provided by a treatment under study at the same level, regardless of age, severity of disease, or level of disability. ICER reports include both measures so that readers can examine how their use does or does not affect the results of the analysis.
7.	We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities. It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color. With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain.	As mentioned above, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. When applied--as in all of ICER's cost-effectiveness analyses—to an incremental comparison of a treatment of interest to an alternative, the evLY produces an estimate of quality of life equivalent to that of the general population during any additional years of life, thereby avoiding concerns that future years of life will be somehow undervalued. While the utility estimate does come from general population survey data, we are unclear why PIPC takes issue with this, particularly because PIPC also criticizes the use of patient-specific utility data in comment 4 above. We also note that none of the citations PIPC offers in support of arguments against the QALY and evLY address their stated concerns, as one (Paulden 2017) focuses on NICE's cost-effectiveness threshold vs. health system opportunity costs, another (Paulden 2024) describes a specific challenge with the evLY *only* in the context of a reassessment in a given disease when the standard of care has changed, and a third (Nord 1999) describes a framework that evLY development was drawn directly from.

8.	**Conclusion** ICER continues to rely on dated and simplistic modeling structures that do not provide a clear picture of real value the patient. We encourage ICER to revise its model to include more elements of value and better methods to meaningfully reflect patient experience on treatment.	The goals of modeling are, of course, to simplify complex processes so as to provide useful answers. We believe our models provide valuable input to discussions of fair pricing for therapies.

References

1. Xie F, Zhou T, Humphries B, Neumann PJ. Do Quality-Adjusted Life-Years Discriminate Against the Elderly? An Empirical Analysis of Published Cost-Effectiveness Analyses. *Value in Health*. 2024;